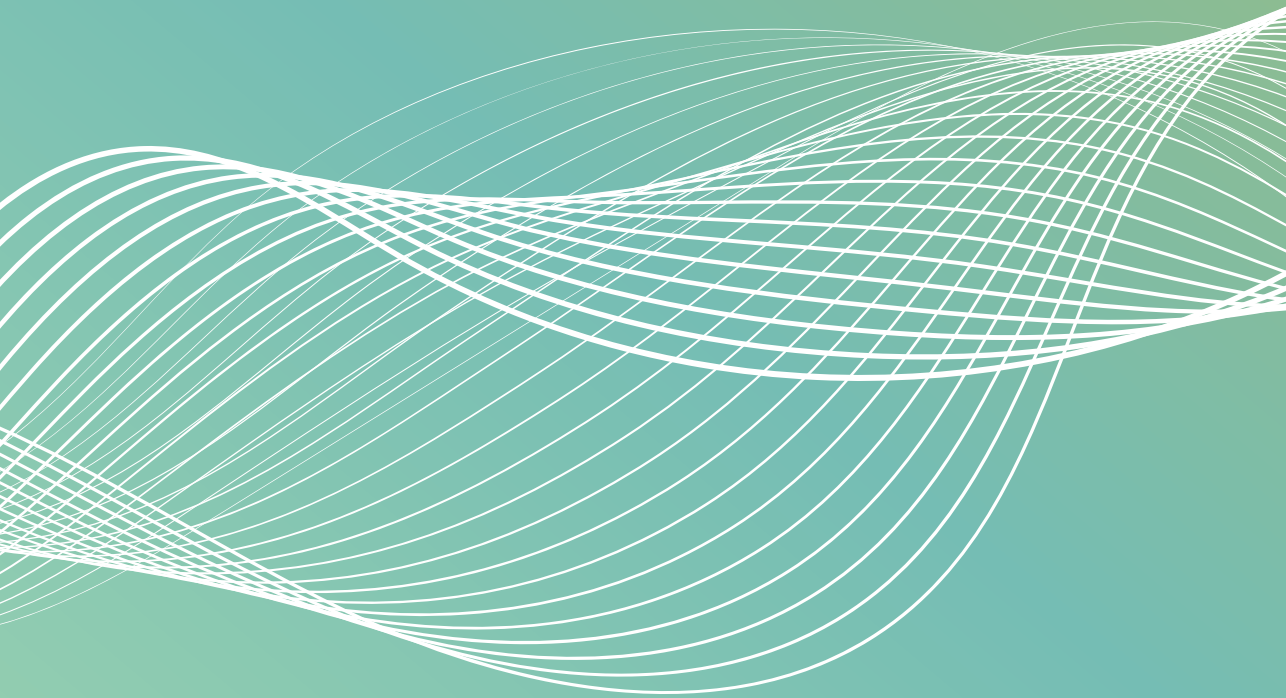


Psychological problems in cancer patients from a clinical as well as an economic perspective



Florie van Beek

**Psychological problems in cancer patients from
a clinical as well as an economic perspective**

Florie Eline van Beek

VRIJE UNIVERSITEIT

Psychological problems in cancer patients from a clinical as well as an economic perspective

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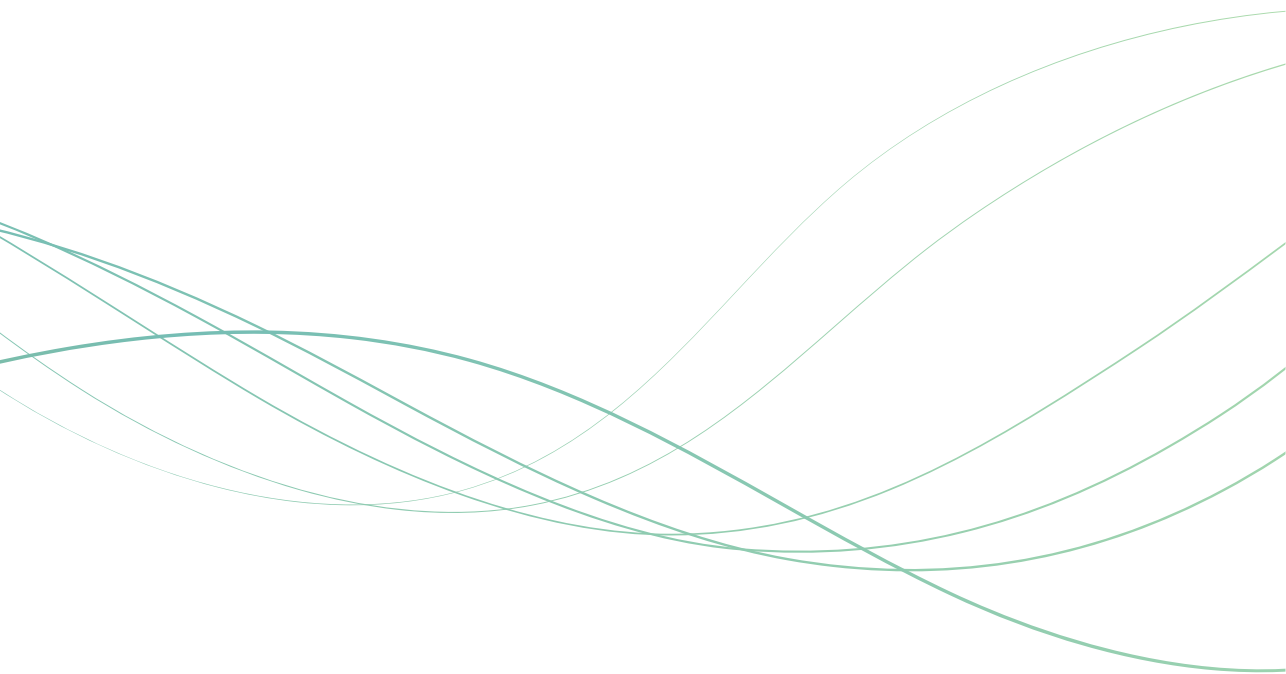
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Chapter 1

General introduction



General introduction

Worldwide the incidence of cancer is growing. It was estimated that 19.3 million people were newly diagnosed in 2020¹. Fortunately, an increasing number of people nowadays can be treated successfully due to advances of early detection and better treatment options¹. More than 65% of cancer patients become long term survivors¹. However, there is also empirical evidence that cancer patients have to deal with psychological problems related to cancer and its treatment from diagnosis to (long) term-follow up²⁻⁷. Approximately up to half of all cancer patients experience psychological distress and approximately one-third of cancer patients is affected by any psychiatric disorder such as depression, anxiety, or adjustment disorder^{8, 9}.

In this thesis, the following psychological problems are addressed: psychological distress, symptoms of depression, symptoms of anxiety, fear of cancer recurrence, and an adjustment, anxiety and depression disorder. This introduction includes background information on 1) cancer epidemiology and cancer treatment, 2) adjustment to cancer, 3) psychological problems in cancer patients, and 4) the economic impact of psychological problems in cancer patients. Existing knowledge on psychological problems among cancer patients from a clinical as well as economic perspective are summarized and the aims and outline of this thesis are described.

Cancer epidemiology and cancer treatment

In the Netherlands 115.000 people were newly diagnosed with cancer in 2020¹⁰. The most common cancer types among women are cancer of the breast (24%), melanoma (19%), lung (12%), colorectal (10%), lymph node and leukemia (8%) and uterus (4%). Among men, the most common cancer sites include prostate (21%), melanoma (19%), lung (12%), colorectal (10%), lymph node and leukemia (9%)¹¹. Incidence rates of cancer are increasing due to changes in risk factors such as lifestyle and life circumstances^{12, 13}. Risk factors of cancer include tobacco use, being overweight, increased alcohol consumption, excessive exposure to ultraviolet radiation and an inactive lifestyle¹⁴. Also genetic predisposition influences the occurrence of cancer¹⁵. The GLOBOCAN which is an online database providing global cancer statistics and estimates of incidence and mortality in 185 countries for 36 types of cancer, estimated that 28.4 million new cancer cases will be diagnosed by 2040¹.

The treatment of cancer patients is interdisciplinary and based on tumor location, TNM stage, preferences of the patient, and the overall health condition of the patient¹⁶. TNM is defined by "size of primary tumor" (T), "degree of spread to regional lymph nodes" (N) and "presence of distant metastasis" (M) and addresses the anatomic tumor extent¹⁷. Cancer treatment is aimed to cure, reduce or prevent cancer symptoms or to

prolong the patients' life. Treatment for cancer typically involves surgery, radiotherapy, chemotherapy, hormone therapy or targeted therapy. Often a combination of treatments is offered¹⁸.

Part of this thesis will focus on head and neck cancer patients as it has been shown that head and neck cancer patients in particular are prone to psychological problems^{7, 19-21}. Due to the visibility and the impact on functions such as breathing, swallowing, speaking, and facial appearance it has been shown to be a physically and psychologically demanding disease²²⁻²⁴. Head and neck cancer represent 3% of all cancer types and encompasses tumors in the oral cavity, oropharynx, hypopharynx and larynx.

The psychological impact of cancer

After a severe diagnosis such as cancer it is common that patients experience intense emotions. The uncertainty of such a diagnosis may lead to feelings including loss of control, death, fear of disability, disfigurement, and the loss of previously held roles in life. Also feelings of sadness, sense of a shock or decreased confidence in body often occur²⁵. Most patients are able to accommodate to their changing health circumstances by protecting factors such as resilience or support of friends and family, and can re-establish a sense of emotional equilibrium. Some cancer patients even report to derive more meaning in life from cancer experiences, experience life more fully in the present, feel a greater appreciation for life, or reprioritize their lives and/or improve health behavior^{26, 27}. On the other hand, cancer patients may experience severe psychological distress and increased symptoms of depression and anxiety which negatively affect a patient's life (e.g. work or study, social relations)²⁸. Compared to healthy individuals, patients with cancer are at increased risk for psychological distress²⁹⁻³¹. Younger age, a history of psychiatric disorder, current depression, or substance use disorder, cognitive impairment, severe comorbid illnesses, uncontrolled symptoms, communication barriers, or social issues (living alone, having young children, prior trauma and/or abuse) are risk factors of psychological problems in cancer patients³². In this thesis, psychological problems refer to psychological symptoms and psychiatric disorders (Table 1). Psychological problems as measured with a patient reported outcome measure (PROM) exceeding its cut-off point, are defined as psychological symptoms. Psychological problems measured by means of a clinical diagnostic interview based on the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) and meeting the criteria for a disorder, are defined as a psychiatric disorder.

Table 1. Overview of terminology and outcome measurements.

Definition in this thesis	Definition in this thesis	Definitions in the literature	Measurements
Psychological problems	Psychological symptoms	Distress	HADS, Impact of Event Scale, DT, K6, K10
		Symptoms of anxiety	HADS, GAD-7, STAI, PROMIS Anxiety, PHQ-4
		Symptoms of depression	HADS, PHQ-9, CES-D, GDS, PROMIS, Back Depression Inventory II
		Fear of cancer recurrence	FCRI-SF, CARS, FoP-Q-SF, CWS
	Psychiatric disorder	Adjustment disorder	CIDI, SCID
		Anxiety disorder	CIDI, SCID
		Depression disorder	CIDI, SCID

Abbreviations: Hospital Anxiety and Depression Scale, (HADS); General Anxiety Disorder-7,(GAD-7); State-Trait Anxiety Inventory, (STAI); Patient Health Questionnaire-4,(PHQ-4); Fear of Cancer Recurrence Inventory – Short Form, (FCRI-SF); Concerns About Recurrence Scale, (CARS); the Fear of Progression Questionnaire - Short Form, (FoP-Q-SF); composite international diagnostic interview, (CIDI); Structured Clinical Interview for DSM (SCID); Center for Epidemiologic Studies Depression Scale, (CES-D); Geriatric Depression Scale, (GDS); Kessler, (K); Distress thermometer, (DT); Cancer Worry Scale, (CWS).

Psychological symptoms

As recommended by international cancer care guidelines, screening tools for psychological distress are often implemented in routine cancer care^{28,32}. Screening stools include the National Comprehensive Cancer Network (NCCN) distress thermometer (DT)³³⁻³⁵ and problem list, or the total score of the Hospitality Anxiety and Depression Scale (HADS)³⁶. According to the NCCN, distress is defined as “a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer and its sequel³⁷. Prevalence rates of distress range from 25% to 46%³⁸⁻⁴¹. Distress encompasses problems in daily life (e.g. financial stress), social problems (e.g. relationship), emotional problems (e.g. self-confidence), and physical problems (e.g. body image, sexuality, pain)^{39, 42}. Distress also encompasses symptoms of depression and anxiety³⁷.

Patients with symptoms of depression may experience symptoms such as sadness, feeling hopeless, empty, depressed, loss of interest in activities, loss of concentration, significant weight loss when not dieting or weight gain, sleep disturbances, fatigue or loss of energy, feelings of guilt or worthlessness or feeling like a burden and suicidal thoughts or plans⁴³. Symptoms of depression are estimated to be prevalent in 8% to 24% of cancer patients⁶.

Patients with symptoms of anxiety may experience symptoms such as restlessness, fatigue, concentration problems, irritability, muscle tension, and sleep disruptions⁴³. Symptoms of anxiety are estimated to be prevalent in 14% to 29% of the cancer patients^{5, 44, 45}.

Regarding fear of cancer recurrence, 22% to 87% of cancer survivors reported moderate to high levels of fear of cancer recurrence and 0% to 15% reported high levels of fear of cancer recurrence⁴⁶. Fear of cancer recurrence is defined as a “fear, worry, or concern about cancer returning or progressing”⁴⁷. To a certain extent is fear an expected response to cancer and its sequel⁴⁸. It can even keep patients motivated to treatment adherence and aware of cancer symptoms⁴⁹. However, a high level of fear can lead to problematic behaviors, including anxious preoccupations, avoidance, and excessive checking^{49, 50}.

Psychiatric disorders

In case of elevated distress, and symptoms of depression, anxiety, or fear of recurrence, a patient can be referred for a clinical diagnostic interview to establish a depression, anxiety or adjustment disorder. Fear of cancer recurrence is not a psychiatric disorder in the DSM-V.

According to the DSM-V an adjustment disorder is diagnosed if *a) the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurs within 3 months of the onset of the stressor(s), b) these symptoms or behaviors are clinically significant, c) the stress-related disturbance does not meet the criteria for another mental disorder and is not merely an exacerbation of a preexisting mental disorder, d) the symptoms do not represent normal bereavement, and e) once the stressor or its consequences have terminated, the symptoms do not persist for more than an additional 6 months*. The DSM-V and International Classification of Diseases Eleventh Edition (ICD-11) both classify adjustment disorder as a trauma and stress related disorder, but differ in the timing of onset of symptoms with respect to the stressor. Also, both lack criteria to specify an adjustment disorder in the context of cancer which makes it difficult to determine if the stress response is related to cancer as the discrete stressor⁵¹. To focus on adjustment disorder in the context of cancer, the Dutch guideline committee (2016) defined adjustment disorder in patients with cancer as the combination and interaction of three pillars, namely stressors (e.g. cancer diagnosis, fear of cancer recurrence, physical changes in a patients’ appearance), insufficient protective factors (e.g. resilience, physical health, meaning, social support, autonomy), and the experience of symptoms (e.g. anxiety, depression, fatigue, relation problems, limited work productivity)⁵². Symptoms of anxiety and depression may be present, but are less severe in case of an adjustment disorder compared to a depression or anxiety

disorder. Also, compared to an anxiety and depression disorder, the diagnosis of an adjustment disorder is often more difficult to establish⁵³. The insufficient operational diagnostic criteria have resulted in relatively lack of attention of adjustment disorder in the literature with regard to epidemiology, prevention, and treatment in patients with cancer⁵¹. Adjustment disorder is found to be prevalent in 6% to 19% of cancer patients^{7, 54-56} and in 0.3% to 2% in the general population⁵⁷⁻⁵⁹.

According to the DSM-V⁴³ a major depressive disorder can be diagnosed if *a) at least five depressive symptoms are present most time of the day during the past two weeks, b) the symptoms cause substantial distress or impairment in social, occupational or other important areas of functioning, c) the episode is not a response to the psychological effects of a substance or to another medical condition, d) The disturbance is not better explained by another mental disorder and e) there has never been a manic episode or a hypomanic episode*. Prevalence of a depression disorder among cancer patients is estimated on 13%⁶ and 4% to 13% in the general population⁶⁰.

According to the DSM-V an anxiety disorder can be diagnosed if *a) excessive anxiety and worry occurs more days than not for at least 6 months, about a number of events or activities (such as work or school performance), b) the individual finds it difficult to control the worry, c) the anxiety and worry are associated with three (or more) of the above mentioned symptoms (with at least some symptoms having been present for more days than not for the past 6 months), d) the anxiety cause substantial distress or impairment in social, occupational, or other important areas of functioning, e) the disturbance is not attributable to the physiological effects of a substance or another medical condition and f) the disturbance is not better explained by another mental disorder*⁴³. Prevalence rates of an anxiety disorder are estimated on 10%⁸ and 2% in the general population⁶¹.

Economic impact of cancer

The total costs of cancer were 199 billion euro in Europe in 2018. These costs included healthcare costs such as costs of cancer diagnosis, treatment and supportive care, and costs of morbidities related to cancer, and other societal costs such as informal care costs and productivity loss costs⁶². As the total healthcare costs of cancer have increased in the last two decennia with almost 50%, corrected for inflation, it is important to investigate the added value (i.e. patients health outcomes, costs savings) of spendend societal money related to cancer.

Carlson and Bultz⁶³ have previously hypothesized that patients with cancer and psychological problems make more use of healthcare (i.e. besides mental healthcare only) than patients with cancer without a psychological problem. Also, literature has shown that patients with psychological problems are less likely to adhere to cancer

treatment or lifestyle recommendations, which may affect their treatment effectiveness and in turn may increase healthcare use⁶⁴. Furthermore, it is hypothesized that psychological problems in cancer patients are associated with lost work productivity and more informal care use^{65, 66}. Psychological problems among cancer patients are thus hypothesized to result in high economic costs from both a healthcare and societal (e.g. absence from work and informal care use) perspective.

However, a detailed systematic overview of the economic consequences of psychological problems in cancer patients is lacking. Also, it hasn't previously been investigated whether costs only exist in specific domains of healthcare use categories. Informal care and lost work productivity in relation to psychological problems are also warranted for further research as these are still understudies subject¹¹.

Aim of this thesis

Summarizing the existing evidence as described above, there is substantial evidence that psychological problems occur in cancer patients. More insight is needed on the course of psychological problems over time from diagnosis to long-term follow-up, especially among high risk cancer populations. Compared to distress, anxiety, depression, and fear of recurrence, evidence on the prevalence of adjustment disorder lags behind. Furthermore, previous studies suggest that psychological problems are associated with higher costs. However, detailed insight into economic consequences (e.g. healthcare use, informal care and work productivity) of psychological problems in cancer patients is still lacking. The main aim of this thesis is to provide insight in psychological problems among cancer patients from a clinical as well economic perspective.

To fulfill the above mentioned research gaps, the clinical-related aims are to:

- 1) investigate the course of symptoms of anxiety and depression over time from diagnosis up to two years after treatment among head and neck cancer patients, in relation to possible risk factors.
- 2) investigate the prevalence of adjustment disorder among mixed cancer patients and possible risk factors and the uptake of psychological treatment.

From an economic perspective this thesis aims to:

- 1) systematically review associations between psychological problems and healthcare and societal related resource utilization and costs among mixed cancer patients.
- 2) investigate the relation between psychological problems (symptoms of anxiety and depression, and fear of cancer recurrence, and an anxiety disorder and depression disorder) and economic consequences (healthcare use and costs and informal care

use and costs) from baseline up to 2 years after treatment among head and neck patients.

Outline of this thesis

First, the systematic review is described that aimed to obtain up-to-date detailed insight into the association between psychological problems and healthcare utilization, work productivity and costs among mixed cancer patients (**Chapter 2**). Subsequently, a prospective cohort study was carried out on the course of symptoms of anxiety and depression from diagnosis up to 2 years follow-up and its associated factors among head and neck cancer patients (**Chapter 3**), followed by a study on the association between psychological problems and healthcare and informal care utilization and costs in head and neck cancer patients, taking into account the main research gaps identified by the systematic review (**Chapter 4**). **Chapter 5** describes the study protocol of a randomized controlled trial on the prevalence of adjustment disorder among mixed cancer patients, and the uptake, effectiveness, cost-utility and budget impact of tailored psychological treatment targeting adjustment disorder. In **Chapter 6**, the prevalence and risk factors of adjustment disorder in mixed cancer patients was investigated, as well as the uptake of psychological treatment. Finally, in **Chapter 7** results of all studies in this thesis are discussed. In addition, strengths and limitations of this thesis, and implications for clinical practice and recommendations for further research are provided.

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Chapter 2

Psychological problems among cancer patients in
relation to healthcare and societal costs:
a systematic review

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Summary

Purpose

This study systematically reviewed the association of psychological problems among cancer patients with healthcare and societal resource use and costs.

Methods

PubMed, PsycINFO, and Embase were searched (until 31-01-2021) for studies on psychological symptoms (anxiety, depression, distress, fear of recurrence) or psychiatric disorders (anxiety, depression, adjustment) and healthcare use (e.g. mental, inpatient healthcare), economic losses by patients and family, economic losses in other sectors (e.g. absence from work), and costs. The search, data extraction, and quality assessment were performed by two authors.

Results

Of the 4157 identified records, 49 articles were included (psychological symptoms (n=34), psychiatric disorders (n=14), both (n=1)) which focused on healthcare use (n=36), economic losses by patients and family (n=5), economic losses in other sectors (n=8) and/or costs (n=13). In total, for 12 of the 94 associations strong evidence was found. Psychological symptoms and psychiatric disorders were positively associated with increased healthcare use (mental, primary, inpatient, outpatient healthcare), losses in other sectors (absence from work), and costs (inpatient, outpatient, total healthcare costs). Moderate evidence was found for a positive association between (any) psychiatric disorder and depression disorder with inpatient healthcare and medication use, respectively.

Conclusions

Psychological problems in cancer patients are associated with increased healthcare use, healthcare costs and economic losses. Further research is needed on psychological problems in relation to understudied healthcare use or costs categories, productivity losses, and informal care costs.

Background

Psychological problems such as symptoms of anxiety, symptoms of depression, psychological distress and fear of cancer recurrence are commonly reported in cancer patients¹⁻³. In case of severe problems a psychiatric disorder may be present. Approximately 11-19% of all cancer patients have a major depression disorder, anxiety disorder or adjustment disorder⁴. These psychological problems may, besides influencing a patients' health-related quality of life⁵, also have economic consequences⁶.

As previously hypothesized by Carlson and Bultz⁶, cancer patients with psychological problems may not only have increased mental healthcare use, they may also make more use of other domains of healthcare such as general practitioner visits or hospitalization. Patients with psychological problems are less likely to adhere to cancer treatment or lifestyle recommendations, which may affect their treatment effectiveness and in turn may increase healthcare use⁷. Also, cancer patients with psychological problems are at higher risk of developing comorbidities (e.g. diabetes and cardiovascular disease)^{8,9}, which may result in higher healthcare use. Besides higher healthcare use, psychological problems may also impact on economic losses by patients and their family themselves (e.g. out of pocket purchases or received informal care)⁶ and economic losses in other sectors for example productivity losses due to absence from work (i.e. sick leave) or decreased work productivity^{10,11}. Psychological problems among cancer patients are thus hypothesized to result in high economic costs from both a healthcare and societal perspective.

It is important to gain detailed insight into these economic consequences of psychological problems among cancer patients, as healthcare costs and other societal costs of cancer are already high¹², and decisions have to be made on allocation of limited healthcare resources. Recently a systematic review (2018)¹³ on 10 studies up to December 2017 investigated the relation between psychiatric disorders and healthcare costs among cancer patients. This systematic review revealed that psychiatric disorders are associated with increased healthcare use and costs across all phases of the cancer trajectory. This systematic review was, however, limited to studies from the United States and did not include studies on psychological symptoms or studies that investigated economic losses of patients, their family or other sectors (e.g. productivity losses). In addition, two systematic reviews investigated factors associated with return to work after cancer diagnosis among cancer patients^{14,15}. However these two reviews did not specifically focus on the economic consequences of the association between psychological problems and return-to-work (i.e. the actual time absent from work).

No systematic review has, so far, focused on the association between psychological problems (including both psychological symptoms and psychiatric disorders) and

all potentially related healthcare and societal resource use and costs among cancer patients. Therefore, the aim of this study was to systematically review associations between psychological problems (anxiety, depression, fear of cancer recurrence, distress, adjustment to cancer) and healthcare and societal related resource use and costs among cancer patients. Results are relevant both from the perspective of cancer patients and their families, as well as their employers (productivity), and the healthcare system with respect to reimbursement of psychological treatment for cancer patients.

Methods

Literature search

PRISMA guidelines were used to conduct and describe this systematic review¹⁶. A comprehensive search was conducted in PubMed, Embase, and PsycINFO from inception up to 31-01-2021. Our search strategy included combinations of keywords, MeSH terms and synonyms which were adapted for each database search, related to three main topics: 1) cancer patients, 2) psychological problems (i.e. psychological symptoms including anxiety symptoms, depressive symptoms, distress and fear of cancer recurrence and psychiatric disorders including anxiety disorder, depression disorder and adjustment disorder) and 3) the use or costs of healthcare or societal resources (e.g., visits to the general practitioner, medication use, inpatient costs, informal care costs, productivity losses).

A detailed description of the search strategy is available in Appendix 1. An information specialist from the medical library provided advice on the literature search. Additionally, reference lists from included articles were manually searched and authors were asked for additional studies.

Study inclusion and exclusion criteria

Research studies were included if:

- 1) they investigated the association between psychological symptoms (i.e. symptoms of anxiety or depression, distress, or fear of cancer recurrence) or a psychiatric disorder (i.e. anxiety disorder, depression disorder or adjustment disorder) and the use or costs of healthcare or societal resources;
- 2) they included adult cancer patients (age \geq 18 years) only; and
- 3) full text was available in English or Dutch.

Research studies were excluded if they:

- 1) presented descriptive statistics on the use or costs of healthcare or societal resources in a certain cancer population without investigating its association with (level of) psychological problems;

- 2) measured work ability or work performance instead of lost working hours;
- 3) measured return-to-work (yes/no) without insight on time absent from work;
- 4) measured return-to-work among cancer patients who were not of working age (i.e. included both patients of working age and those who were retired) or
- 5) were reviews

No limits were set for year of publication.

Selection process and quality assessment

After removing duplicates, two independent reviewers (FB and LW) screened all identified records based on title and abstract. Records that were not relevant based on the screening were excluded. Subsequently, the full-text article of potentially relevant records were screened for eligibility using the inclusion and exclusion criteria. In case of disagreement, the full-text article was discussed by the two reviewers, and when needed a third author (FJ) was involved to meet consensus.

The quality of the included study was assessed with an 11-item quality assessment scoring list based on Hayden et al.¹⁷ and Drummond et al.^{18,19}. This list comprises four domains: study population, study attrition, data collection and data analysis. Each item was scored positive ("1") or negative ("0"). In case information to evaluate an item was lacking, that item was scored negative as well. In case an item was not applicable, that item was scored as 'not applicable (N/A)'. A total score was calculated by summing the item scores, resulting in a score ranging from 0 (lowest quality) to 11 (highest quality). The quality assessment was conducted independently by two reviewers (FB and LW). In case of disagreement, the item was discussed by the two reviewers, and when needed a third author (FJ) to meet consensus. In line with previous studies^{20,21}, the article was rated "high quality" when an article was assigned at least 70% of the total score.

Data extraction

All studies eligible for inclusion were read thoroughly to extract data. For the data extraction a standardized collection form was used including: general information (first author, publication year, country), study design, study population (number of patients included, cancer site, relevant inclusion and exclusion criteria), psychological outcome and its measurement, use/costs outcomes and its measurement, and results (e.g. odds ratio, risk ratio, differences in mean). Based on the Dutch cost guideline of the National Healthcare institute²², the use/cost outcome were, categorized into 1) healthcare use (e.g. medical specialist visits, length of hospital stay, medication use), 2) economic losses by patients and family (e.g. time expenses for providing informal care, travel costs, out of pocket payments) and 3) economic losses in other sectors (e.g. absenteeism from work). In addition, a fourth category was added in which healthcare

use, losses by patients and family, and/or losses in other sectors were valued in monetary units. Based on the associations found in the literature, the four categories were further divided into subcategories including healthcare use (i.e. mental healthcare, supportive non-mental healthcare, primary care, oncology-related healthcare, inpatient care, outpatient care, medication, and other healthcare use), economic losses by patient and family (i.e. complementary and alternatively medicine use (CAM), healthcare use of spouses, and lost work productivity of spouses), economic losses in other sectors (i.e. return-to-work) and losses in monetary units (i.e. mental healthcare, inpatient, outpatient, medication, total healthcare, absenteeism and presentisms (costs), out of pocket costs, and other costs) (Figure 1).

Figure 1. Categorization of healthcare and societal resource use and costs.

1. Healthcare use^a <ul style="list-style-type: none">* Mental healthcare* Supportive non-mental healthcare* primary care* Oncology related healthcare* Inpatient care* Outpatient care* Medication* Other healthcare use	4. Healthcare use, losses by patients and family and losses in other sectors measured in monetary units <ul style="list-style-type: none">* Mental healthcare* Inpatient care* Outpatient care* Medication* Total healthcare* absenteeism and presenteeism costs* Out of pocket costs* Other costs
2. Economic losses by patients and family <ul style="list-style-type: none">* Complementary and alternatively medicine use* Healthcare use of spouses* Lost work productivity of spouses	
3. Economic losses in other sectors <ul style="list-style-type: none">* Return to work	

^a For the subcategorization we were dependent on the description provided in the individual studies. Healthcare resource utilization was only categorized in the subcategory ‘oncology-related healthcare’ if this matched the definition used in the corresponding article. In all other cases the investigated association was categorized in a broader subcategory, e.g. ‘outpatient care’.

Statistical methods and level of scientific evidence

We used a best-evidence synthesis to estimate the level of evidence for the investigated associations between psychological problems and healthcare use, economic losses by patients and family, economic losses in other sectors, and total costs, as used in previous studies^{20, 21, 23}. The levels of evidence were 1) strong if an association was consistently supported by at least two high quality studies, 2) moderate if an association was consistently supported by at least one high-quality study and at least one low-quality study or if a factor was consistently supported by at least two low-quality studies, and 3) inconclusive, if an association was supported by only one study, results were inconsistent or did not show an indication for a positive or negative association.

Results

Identification and selection of studies

In total 4157 articles were yielded by PubMed, Embase and PsycINFO. Of these studies 272 were selected for full text review (Figure 2). In total 49²⁴⁻⁷¹ studies fulfilled the eligibility criteria and were included in this systematic review. The majority of the studies focused on healthcare use (n=36)^{24, 25, 27-29, 31, 33-35, 37-39, 41-48, 51, 53, 54, 56-62, 64, 67, 69-72} followed by studies on costs in monetary units (n=13)^{26, 29, 34, 36, 38, 42-44, 48, 53, 55, 57, 61}, economic losses in other sectors (n=8)^{30, 32, 40, 49, 63, 65, 66, 68} and economic losses by patients and family (n=6)^{28, 29, 50, 52, 64, 69}. Thirteen studies^{28, 29, 34, 38, 42-44, 48, 53, 57, 61, 69} focused on two or more of these categories (e.g. healthcare use and costs in monetary units), resulting in a total sum greater than 49 studies. In Table 1a-1d the characteristics of the included studies are presented according to healthcare use (Table 1a), economic losses by patients and family (Table 1b), economic losses in other sectors (Table 1c) and costs in monetary units (Table 1d).

Figure 2. PRISMA flow diagram.

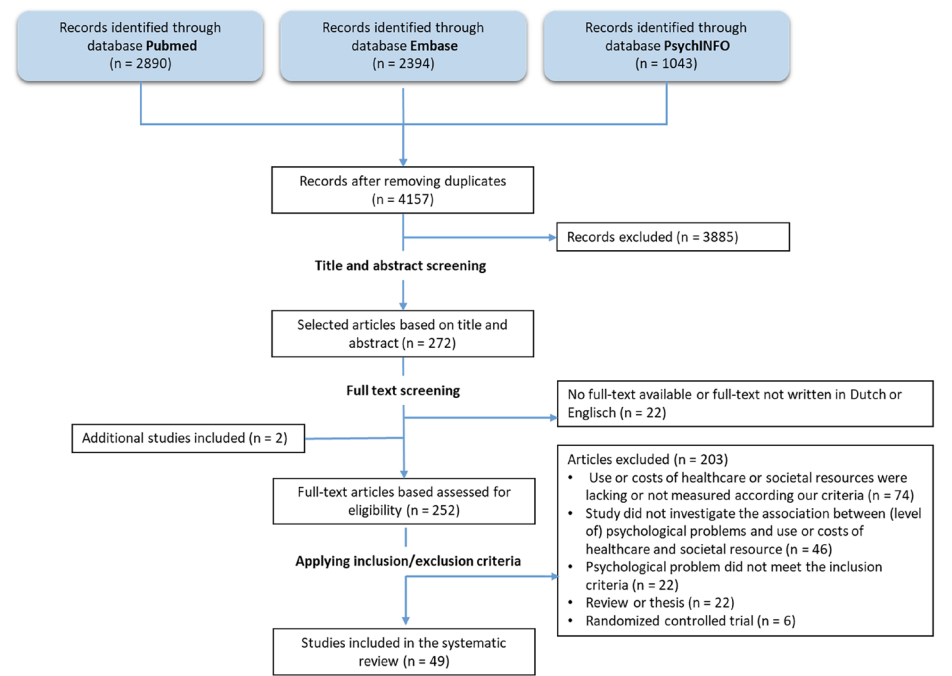


Table 1a. Overview of articles on the relation between psychological problems and healthcare use among cancer patients (*this table is shown over two pages*)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results ^b
				Mixed cancers	Mixed cancers		
Cagle, 2020, US	Prospective cohort	Mixed cancers (467)	+ died between 2012 and 2014 + older than 50 years	Depression CES-D	Hospice use (<i>yes/no</i>)	Interviews with the person most familiar with the decedent	Not significant Depression and hospice use
Champagne, 2018, Canada ^a	Longitudinal (follow-up at 0, 2, 10, 14 and 18 months)	Mixed cancers (955)	+ age between 18 and 80 + first cancer diagnosis non metastatic to be scheduled to receive a surgery - severe psychiatric disorder - diagnosed or treated for sleeping disorder	FCR FCRI-SF (>=13)	Medical professional: specialist physician, general practitioner, nurse, pharmacist, homeopath/ osteopath, massage therapist Psychosocial professional: social worker psychologist, psychiatrist, physiotherapist Psychotropic medication: Anxiolytics/hypnotics, antidepressants (<i>yes/no</i>)	Study-specific questionnaire	Significant FCR and medical professionals (F=4.09, P=0.04) FCR and psychosocial professionals (F=5.23, P<0.0001) FCR and Anxiolytics/hypnotics (F=9.88, P=0.0017) FCR and antidepressants (F=5.23, P=0.0499)
Compen, 2018, Netherlands ^a	Cross-sectional	Mixed cancers (245)	+ HADS ≥ 11 + stable 3 months psychotropic medication + current active anticancer treatment - severe psychiatric morbidity - previous mindfulness intervention	Anxiety, depression and adjustment disorder, psychological distress HADS, SCID-I	Mental health care: social workers, psychologists, and psychiatrists Primary health care: GP, occupational physicians, and physical and occupational therapists Somatic health care: medical outpatient clinics, ED, day health care units, and overnight hospital stays	TiC-P	Significant Depression disorder and mental healthcare (IRR= 1.71 (1.11-2.62)) (P<0.01) Adjustment disorder and mental healthcare (IRR=1.77 (1.00-3.10)) (P<0.05) Distress and mental healthcare (IRR=1.09 (1.06-1.12)) (P<0.01) depressive symptoms and mental health (IRR=1.14 (1.09-1.19)) (P<0.01) Anxiety symptoms and mental health (IRR=1.12 (1.07-1.18)) (P<0.01) Depressive symptoms and primary healthcare use (IRR=1.04 (1.00-1.08)) (P<0.05) Not significant Depression, anxiety, adjustment disorder with primary and somatic healthcare use. Distress and anxiety with and primary and somatic care. Depressive symptoms and somatic healthcare use.
Faller, 2017, Germany	Cross-sectional	Mixed cancers (4020)	+ age between 18 and 75 + evidence of a malignant tumor	Anxiety, depressive symptoms, distress DT (≥5), PHQ (≥9), GAD-7 (≥10)	Utilization of psychological care (<i>yes/no</i>), counseling support (<i>yes/no</i>)	Study-specific questionnaire	Not significant Distress and utilization psychological care (OR=1.01 (0.95-1.06)) Depression and utilization psychological care (OR=1.03 (1.00-1.07)) Anxiety and utilization psychological care (OR=1.06 (1.02-1.10))
Hamilton, 2019, USA	Prospective cohort	Mixed cancers (893)	+ having a cancer related medical appointment + during treatment, standard clinical care	Distress DT (>6)	Service use: social work, psychologist, nutritionist, or chaplain, psychological service use on any inpatient hospitalization	Electronic medical record from the past twelve months (<i>yes/no</i>) (<i>frequency visits</i>)	Significant Distress (continue) and service use (B=0.03) (P=0.007) Distress (<i>yes/no</i>) and service use (B=0.21) (P=0.004) Distress (>6, continue) and social work (P=0.001) Distress (>6, continue) and dietetics utilization (P=0.004) Not significant Distress (>6, continue) and chaplaincy service and psychology service
Jacobsen, 2016, USA	Part of Longitudinal (cross-sectional)	Advanced mixed cancer patients (123)	+ older than 20 years + identified informal care giver + diagnosis of advanced cancer (presence of distant metastases and failure of first-line chemotherapy	Major depressive disorder SCID	Mental health service use	Study-specific questionnaire	Significant Depression and mental health service use (OR = 16.07 (1.68 - 153.77))
Jeffery, 2012, US ^a	Cross-sectional	Mixed cancers (11014)	+ at least 1 healthcare service record in fiscal year 2006 + 18 years or older + survived at least 2 years after their initial cancer treatment - nonmelanoma skin cancer	Depression Medical record (ICD-9)	Service use: inpatient stays, lengths of inpatient stays, number of outpatient visits (number) Medication: prescriptions (number)	Medical record	Significant Depression (<i>yes/no</i>) mean number of stays (0.41 (0.9) vs 0.12 (0.44)) Depression (<i>yes/no</i>) mean number of bed days (3.15 (14.39) vs 0.64 (4.3)) Depression (<i>yes/no</i>) mean number outpatient visits (33.66 (28.84) vs 18.69 (18.29)) Depression and number of prescriptions (45.28 (33.73) vs 24.46 (23.51)) All P-values < 0.05

Table 1a. Continued

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results ^b
Lo, 2013, Canada	Retrospective, observational (one year before measurement of depression, 1 year after depression diagnosis)	Mixed cancer patients (680)	+ 18 years or older + confirmed diagnosis of stage 4 gastrointestinal, breast, gynecologic, or genitourinary cancer, or stage IIIA, IIIB, or IV lung cancer + 451 (173-1036) (median) days since diagnosis - cognitive impairment documented - carcinoid or neuroendocrine tumors	Depression Back Depression Inventory II (≥ 20)	Physician visits: primary care mental health, primary care non-mental health and oncology	Administrative databases	Significant Look-back period (one year before measurement of depression) Depression and primary non mental health care (RR=1.21 (1.00-1.50)) (P=0.005) Look-forward (one year after measurement of depression) Depression and primary care mental health visits (RR=2.35 (118-4.66)) (P=0.015) Depression and oncology visits (RR=-0.78 (0.65-0.94)) (P=0.008)) (negative association) Not significant Look-back period (one year before measurement of depression) Depression and primary care mental health visits, oncology visits Look forward period (one year after measurement of depression) Depression and primary non-mental health visits,
Mausbach, 2017, USA	Retrospective cross-sectional	Mixed cancer (5055)	None	Depression Medical record (ICD-9)	Non-mental healthcare visits (number), ED visits, inpatients healthcare use (hospitalization and 30-day rehospitalization)	Medical record (the total number of contacts was calculated as the sum of use categories)	Significant Depression and healthcare visits (RR=1.76 (1.61-1.93)) (P=0.001) Depression and ED visits (OR=2.45 (1.97-3.04)) (P=0.001) Depression and hospitalization (OR=1.81 (1.49-2.20)) (P<0.001) Depression and 30-day rehospitalization (OR=2.03 (1.48-2.79)) (P<0.001)
Mausbach, 2020, California ^a	Retrospective cohort	Mixed cancers (13426)	+ diagnosis of cancer in 2014 + 18 years or older + at least one healthcare claim within 1 year of cancer diagnosis	Anxiety, Depression (electronic medical record)	Healthcare use (ED visits, inpatient hospitalization)	Electronic medical record	Significant Depression and ED visits (B(SE)=0.817 (0.074)) (P<0.001) Depression and hospitalization (B(SE)= 0.584)) (0.076) (P<0.001) Anxiety and ED visits (B(SE)=0.851 (0.073)) (P<0.001) Anxiety and hospitalization (B(SE)=0.704 (0.074)) (P<0.00)
Pan, 2015, USA ^a	Cross-sectional	Mixed cancer patients (4766)	+ older than 21 years + reported with cancer in 2006-2009	Depression Medical record (ICD-9)	Inpatient (yes/no), outpatient (yes/no), ED (yes/no), Prescription Drug (yes/no), and other health care Services (yes/no)	Study specific questionnaire	Significant Depression and ED visits (AOR=1.46 (1.17-1.82)) (P<0.001) Not significant Depression and inpatient use and other service use
Rana, 2019, Australie	Cross-sectional	Mixed cancers (517)	+ older than 15 years + diagnosed with any type of cancer	Distress K-10 (four categories:1= no, 2= mild, 3= moderate, 4= severe distress)	Doctor visits (yes/no), hospital admissions (>1)	Study specific questionnaire	Significant Distress a little (compared to never distress) and doctor visits (OR= 1.88 (1.02-3.47)) (P=0.04) Distress and doctor visits (B= 0.144 (0.110-0.178)) (P=0.00) Not significant Distress sometimes and most times compared to never and doctor visits Distress most times, sometimes, a little compared to never and hospital admissions Distress and hospital admissions
Sarker, 2015, Germany	Cross-sectional	Mixed cancers (335)	+ 18 years or older + a malignant tumor (all tumor entities and disease stages) + 12 (21.3-228) (mean, SD range) months after cancer diagnosis, - presence of psychical, psychological and/or cognitive impairments	FCR and anxiety FoP-Q-SF (high FCR >34), GAD-7 (categorical)	Psychological support services, medical support services, complementary support services, spiritual and religious support services, and other support services (yes/no)	Self-report over one year	Not significant FCR and anxiety with psychological support services, medical support services, spiritual and religious support services, and other support services
Trevino, 2019, USA	Cross-sectional	Mixed cancer (1211)	+ 75 years or older with cancer undergoing surgery + who were referred to the geriatric services for preoperative evaluation + underwent elective surgery with a length of stay of >3 days, and received at least 30 days of postoperative follow-up	Distress, depression DT((>4), GDS (≥ 1))	Mental healthcare use (social work, psychology, and/or psychiatry clinicians and the patient and/ or family during the postoperative stay)	Electronic medical record	Significant Distress and mental healthcare use (OR= 1.72 (1.16-2.56)) [P=.007]) Not significant Depression and mental healthcare use (OR= 1.10 (0.73-1.64)) (P=0.65))
Lebel, 2013, Canada	Cross-sectional	Breast, prostate, colon, or lung cancer (231)	+ 18 years or older + diagnosed in the past 10 years + 7.2 (2.4) (mean, SD) years since diagnosis	FCR FCRI (severity subscale >13)	Outpatient clinic, medical specialist, another healthcare provider, ER, admitted to hospital over the past 6 months (<i>visits</i>) and medication taken in the past week)	CBMTG Healthcare utilization questionnaire	Significant FCR and outpatient visits (B=0.16) (P=0.025) FCR and ER visits (B=0.14) (P=0.047) Not significant FCR and MS visits, medication use, mental healthcare visits and number of overnight visits.

Table 1a. Continued

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results ^a
				Breast cancers	Breast cancers		
Fox, 2013, USA ^a	Retrospective	Breast cancer (40202)	+ 18 years or older + diagnosis of invasive breast cancer + procedure for mastectomy - breast conserving surgery	Psychiatric disorder: depression, GAD, adjustment disorder, panic disorder Medical record (ICD-9)	Prolonged hospitalization (>3 days)	NIS reports (electronic medical record)	Significant Psychiatric disorder and prolonged hospitalization (OR= 1.40 (1.32–1.49))
Keyzer-Dekker, 2012, Netherlands	Cross-sectional	Benign or malignant breast disease (151)	+ referral after mammogram + palpable lump abnormality on a screening mammogram - medical history with breast cancer or psychiatric disease - advanced breast cancer	Anxiety and depression STAI, CES-D (cut-of not mentioned)	Medical specialist and GP (visits), and use of psychosocial healthcare, i.e. psychologist, welfare worker, self-help groups (yes/no) (number visits)	Self-report questions concerning use during first year after diagnosis	Significant Anxiety (low/high level) and psychosocial healthcare use (P=0.004) Not significant Anxiety and medical specialist and GP visits. Depression and psychosocial healthcare use and MS and GP visits
Oleske, 2004, USA	Cross-sectional (retrospective)	Breast cancer (123)	+ women between 21 and 65 and who were expected to survive at least three years + at least one year after treatment + mean time since diagnosis, 3.6 years	Symptoms of depression CES-D (≥16)	Any type of hospitalization overnight for any reason	Survey of 27 items about the frequency of visits in the past year	Significant Depressive symptoms and hospitalization (OR = 1.09 (1.03–1.16)) (p =0.041).
Otto, 2018, USA	Cross-sectional	Early breast cancer survivors (300)	+ 18 years or older + diagnosed within the past 7 years + completed any planned surgeries, chemotherapy, or radiation therapy -recurrence of breast cancer	FCR FCRI	Frequency of office visits, phone calls oncology medical providers and primary care, sought out mental health (yes/no), psychotropic medication (yes/no)	Self-report over the past 3 months	Significant: FCR and oncology visits (RR=1.53 (1.16-2.01)) (P=0.002) FCR and phone calls (RR=2.08 (122-3.54)) (P=0.007). FCR and primary care provider visits (R=1.31, (1.06-1.61)) (P=0.013) Not significant: FCR and primary care phone calls , mental health treatment and psychotropic
Thewes, 2012, Australie	Cross-sectional	Early breast cancer (218)	+ age between 18 and 45 + early breast cancer (stage0-2) + diagnosed at least 1 year ago + completed hospital based treatment, no history of recurrent disease or new primary cancer + 50 months (mean) after diagnosis	FCR FCRI (severity subscale >13) (subscale 0-36)	GP and oncologist visits, other health care usage (professional counselling, participation in support groups and membership of consumer advocacy groups (yes/no)	Self-report over the past 12 months	Significant FCR and GP visits (yes/no) (9.9 (2.3-17.4)) (P=0.01) FRC and mammograms (once or more per year /no) (-18.2 (-29.1;-7.3)) (P=0.001) (negative association) FCR and other screening practices (yes/no) (-10.9 (-20.7;-1.2)) (0.003) (negative association) FCR and current counseling (19.4 (4.8-33.9)) (P=0.009) FCR and support group (10.9 (0.2-21.6)) (P=0.05)
Vachon, 2020, USA	Cross-sectional	Breast cancer (1127)	+ 45 years or younger or age between 55 and 70 years + initial cancer diagnosis at stage I-IIIa + 3 till 8 years post initial treatment at time enrollment study + been treated with an adjuvant chemotherapy regimen - no cancer recurrence	FCR Concerns About Recurrence Scale (CARS) Total Worries Index	Cancer related healthcare use (routine follow-up, visiting healthcare provider, ER), no cancer related healthcare use (visiting healthcare provider, ER)	Study specific questionnaire about healthcare use past 12 months	Significant FCR and routine follow-up care cancer (IRR=1.003, SE=0.01, P=0.02) Not significant FCR and ER (related to cancer; ER (not related to cancer), healthcare provider visits (related to cancer), annual healthcare provider visits (not related to cancer)
				Other single tumor types			
Arts, 2018, Netherlands	Cross-sectional	lymphoma and chronic lymphocytic leukemia (1444)	+ 18 years or older + cancer survivors - no terminal care	Psychological distress HADS (≥13)	Receiving psychological care (yes/no), ≥= 3 GP contact (yes/no), ≥=4 Medical Specialist visit (yes/no)	Study specific questionnaire (recall period of 12 months)	Significant Distress and receiving psychological care (OR=2.19 (1.62-2.98)) (P<0.05)) Distress and contacting GP (OR=2.06 (1.57-2.69)) (P<0.05)) Distress and Medical specialist visit (OR= 1.80 (1.36-2.38)) (P<0.05))
Bhattarai, 2013, UK	Retrospective cohort	Colorectal cancer	+ age between 30 and 100 + registered at a contributing practice	Depression Medical records	GP consults, prescriptions, outpatient and inpatient	Medical records (1year)	Significant: Depression and prescription, inpatient and outpatient (women) Depression and prescription, inpatient and outpatient. (men) Not significant: Depression and GP consultations (women)
Doll, 2016, US	Longitudinal (follow-up at 1, 3, 6 months)	Gynecologic cancer (185)	+ age older than 18 + newly diagnosed gynecologic cancer and planned surgical management. - active chemo or radiotherapy treatment	Anxiety PROMIS Anxiety	Unplanned clinic or ER encounter within 30 days after surgery) (yes/no)	Hospital electronic medical record (30 days)	Not significant Healthcare use (+) group had higher anxiety scores than healthcare use (-) group (58.3 vs. 53.8) (p= 0.06)

Table 1a. Continued

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results ^b
Godby, 2020, US	Cross-sectional	Gastrointestinal cancer (355)	+ 18 years or older + patients who were chemotherapy naïve.	Depressive symptoms PROMIS ((≥60)	ER visits and hospitalization prior year (yes/no), daily medication use past seven days (yes/no)	Cancer & Aging Resilience Evaluation (CARE) survey	Significant Depressive symptoms and daily medication use (OR=2.51 (1.21–5.20)) Not significant Depressive symptoms and ER visits and hospitalization
Holla, 2016,	Cross-sectional	Colorectal cancer (3957)	+ older than 18 years + undergone surgery with or without radiotherapy or chemotherapy - cognitive impairments	Anxious and depressive mood HADS	Supportive care (dietician, oncological nurse, physical therapist, psychologist, completion rehabilitation program) (yes/no), number of visits from GP and Medical doctor) (number of visits)	Study specific questionnaire	Significant Anxiety and dietary care (OR=1.09 (1.06 to 1.12)) (p<0.01) Anxiety and oncological nursing care (OR= 1.07 (1.04 to 1.11)) (p<0.01) Anxiety and physical therapy (OR=(1.06 (1.03 to 1.09)) (p<0.01) Anxiety and psychological care (OR= 1.18 (1.13 to 1.22)) (p<0.01) Anxiety and rehabilitation program (OR=1.08 (1.05 to 1.12)) (p<0.01) Depression and dietary care (OR=1.10 (1.07 to 1.13)) (p<0.01) Depression and oncological nursing care (OR=1.06 (1.03 to 1.10)) (p<0.01) Depression and physical therapy (OR=1.06 (1.03 to 1.09)) (p<0.01) Depression and psychological care (OR= 1.15 (1.11 to 1.20)) (p<0.01) Depression and rehabilitation program (OR=1.06 (1.02 to 1.10)) (p<0.01) Significant Depression in treatment phase and ER visits (OR=3.46 (3.21-3.74)) Depression in post treatment phase and ER visits (OR=1.64 (1.54-1.78)) Depression in treatment phase and hospitalization (OR = 2.76 (2.63-2.88)) Depression in post treatment phase and hospitalization (OR=1.34 (1.29-1.39)) Depression in treatment phase and outpatient visits (OR=1.80 (1.76-1.85)) Depression in post treatment phase and outpatient visits (OR= 1.52 (1.50-1.80)) All compared to no depression
Jayadevappa, 2012, USA ^a	Longitudinal 1 year prior to diagnosis, and 5 year post diagnosis	Prostate cancer (50,147)	+ older than 66 years +1 year prior to diagnosis, and 5 year post diagnosis, in case the patient died, 1 year prior to dead was called terminal phase	Depression Medical record (ICD-9)	Inpatient (length of stay, number of admissions, surgical and diagnostic procedures), out-patient (laboratory testing and emergency room (ER) visits), durable medical equipment, home health services, skilled nursing facility use and hospice care),	SEER-Medicare linked data (1 year prior to diagnosis, and 5 year post diagnosis)	Significant Depression and ambulatory visits (WX2=2765.48) (P<0.0001) Anxiety and ambulatory visits (WX2=1948.34) (P<0.0001) Adjustment disorder and ambulatory visits (WX2=2597.13) (P<0.0001) Depression and number hospital admissions (WX2=38.43) (P<0.0001) Anxiety and number hospital admissions (WX2=38.87) (P<0.0001) Adjustment disorder and number hospital admissions (WX2=8.97) (P<0.0027) Depression and number of hospital bed days (WX2=876.28) (P<0.0001) Anxiety and number of hospital bed days (WX2=932.81) (P<0.0001) Adjustment disorder and number of hospital bed days (WX2=43.25) (P<0.0001)
Jeffery, 2019, USA ^a	Retrospective cross-sectional	Head and neck cancer (2944)	+ age between 18 and 64 + had a primary diagnosis of head and neck cancer + sex of the patients was known + the rank of the military sponsor was enlisted or officer + healthcare was delivered within US	Anxiety, depression and adjustment disorder Military data repository ICD-9	Annual number of ambulatory visits, hospital admission, and hospital bed days)	ICD-9 codes,	Significant Depression and ambulatory visits (WX2=2765.48) (P<0.0001) Anxiety and ambulatory visits (WX2=1948.34) (P<0.0001) Adjustment disorder and ambulatory visits (WX2=2597.13) (P<0.0001) Depression and number hospital admissions (WX2=38.43) (P<0.0001) Anxiety and number hospital admissions (WX2=38.87) (P<0.0001) Adjustment disorder and number hospital admissions (WX2=8.97) (P<0.0027) Depression and number of hospital bed days (WX2=876.28) (P<0.0001) Anxiety and number of hospital bed days (WX2=932.81) (P<0.0001) Adjustment disorder and number of hospital bed days (WX2=43.25) (P<0.0001)

Table 1a. Continued

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)
Laurence, 2017, USA	Retrospective	Head and neck cancer (36 420)	+ 50 years and older - cancers of the lip, salivary glands, nasopharynx and thyroid	Depression Medical record (ICD-9-M)
Lee, 2018, Taiwan ^a	Population-based cohort study retrospectively	Hepatocellular carcinoma (223 matched with non-disorder (anxiety and depression) group)	+ treated between 1996 and 2010 + 18 years or older + history of HHC enrolment in registry for catastrophic illness patient database - patient with anxiety or depression before diagnosis	Anxiety/depression Medical record (ICD-9)
McDermott, 2018, USA	Cross-sectional	Advanced Non-small-Cell Lung cancer (13827)	+ older than 67 years + diagnosed with stage IIIB or IV in 2007-2011 and claims spanning 2007-2013	Depression ICD-9 (diagnosis-time depression/post-diagnosis depression/
Mosher, 2013, USA	Cross-sectional	Lung cancer (165)	+ 18 years or older have/had cancer treatment + 18 (22) months (mean, SD) after cancer diagnosis + not too ill to participate in the study	Anxiety and depressive symptoms HADS (≥9, ≥8)
Niazi, 2018, USA ^a	Cross-sectional	Multiple myeloma (36007)	+ diagnosed between 1991 and 2010 with Multiple myeloma + full medical coverage	Depression ICD-9 (yes/no)

Table 1a. Continued

Healthcare use	Measurement healthcare use	Results ^b
ED visit (<i>ended in admission vs discharge</i>)	Data from Nationwide Emergency Department Sample (NEDS) (2008) (ICD-codes)	Significant <i>head and neck cancer</i> Depression and hospital admission men (PR=1.28 (1.21-1.36)) (P<0.001) Depression and hospital admission women (PR=1.31 (1.20-1.42)) (P<0.001) <i>Larynx/Hypopharynx</i> Depression and hospital admission men (PR=1.21 (1.21-1.30)) (P<0.001) Depression and hospital admission women (PR=1.27 (1.16-1.40)) (P<0.001) <i>Oropharynx</i> Depression and hospital admission men (PR=1.14 (1.06-1.24)) (P<0.001) <i>Oral cavity</i> Depression and hospital admission men (PR=1.56 (1.25-1.94)) (P<0.001) Not significant <i>Oropharynx</i> Depression and hospital admission women (PR=1.08 (0.92-1.27)) (P=0.330) <i>Oral cavity</i> Depression and hospital admission women (PR=1.29 (0.98-1.70)) (P=0.330)
Physician visits and lengths of stay hospital	Administrative claims for reimbursement from the Taiwan Bureau of National Health insurance	Significant Usage 1 years after diagnosis Anxiety/depression and physician visits (diff.= 48.2 (0.3)) (P<0.001) Anxiety/depression and length of stay (diff.= 9.0 (0.4)) (P<0.001) Usage 5 years after diagnosis Anxiety/depression and physician visits (diff.= 91.4 (0.5)) (P<0.001) Anxiety/depression and length of stay (diff.= 15.9 (1.1)) (P<0.001)
Hospice use >3 days and >90 days, >1 inpatient, in-hospital death, >1 ED visits, >1 hospitalizations, or ICU admission in the last 30 days of life, or chemotherapy receipt in the last 14 days of life	Electronic medical record	significant: Post-diagnosis depression and ICU admission (OR=1.18 (1.01-1.37)) Not significant Diagnosis-time depression and inpatient admission, ICU admission, in-hospital death, ED visits and chemotherapy in last 14 days Post-diagnosis depression and inpatient admission, in-hospital death, ED visits and chemotherapy in last 14 days
Mental health services, including psychotherapy/ counseling/ psychotropic medication and support groups, spiritual leader)	Patient reported questionnaire	Not significant Depression and anxiety and mental health use and help of spiritual leader
Inpatient, Outpatient, ambulatory claims	SEER-Medicare (use and costs within the first 6 months after the diagnosis)	Significant Depression and undergoing inpatient (OR=1.41, (1.31-1.53)) Depression and ED (OR=1.37 (1.28-1.47)) Depression and ambulatory care. (OR=1.22 (1.14-1.30)) all P<0.001.

Table 1a. Continued

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results ^b
Nipp, 2017, US	Unclear	Mixed cancer (1036)	+ older than 18 years and palliative + advanced cancer + not treated with curative intent - excluded patients with leukemia and those who were admitted for stem cell transplantation - patients with elective or planned hospital admissions	Depression, anxiety and distress PHQ-4 (>3 per subscale) (continues for distress)	Hospital length of stay, unplanned hospital admissions	Medical record	Significant: Anxiety and time readmission within 90 days (HR=1.059 (1.001-1.119)) (P=0.045). Not significant Depression and anxiety and hospital length of stay. Depression and time to readmission within 90 days
Schuurhuize, 2019, Netherlands	Longitudinal (baseline, after 10, 24 and 48 weeks of treatments)	Metastatic colorectal cancer (349)	+ diagnosis of metastatic colorectal Cancer and started first line systemic treatment	Distress HADS (≥13), DT (≥5)	Psychosocial service utilization (yes/no)	TiC-P	Not significant Depression and Psychosocial service utilization Distress and Psychosocial service utilization
X, Han, 2015, US ^a	Cross-sectional	Mixed cancers (3309)	+ history with cancer + older than 18 years - non melanoma skin cancer	Psychological distress K6 (≥13)	Medical provider visits, number of hospital outpatient visits, number of inpatient discharges, number of emergency department visits, dental visits, number of prescribed medicines)	Survey and contacting medical providers	Significant among mixed cancer Distress (no/yes), hospital outpatient visits 35.3% vs 43.3% (P=0.0153) Distress (no/yes), hospital inpatient discharge 16.0% vs 43.3% (P=0.0005) Distress (no/yes), emergency visits 17.5% vs 35.3% (P<0.0001) Distress (no/yes), dental visits 53.1% vs 27.1% (P<0.0001) (negative) Distress (no/yes), home healthcare visits 5.8% vs 16.2% (P<0.0001) Distress (no/yes, medicine prescriptions 90.6% vs 95.5% (P=0.0011) Significant among breast cancer Distress (no/yes), hospital inpatient discharge 11.7% vs 27.0% (P=0.0184) Distress (no/yes), emergency visits 13.9% vs 29.4% (P=0.0153) Distress (no/yes), dental visits 60.3% vs 38.0% (P=0.0083) (negative) Significant among prostate cancer Distress (no/yes), office based visits 95.7% vs 99.3% (P=0.0195) Distress (no/yes), emergency visits 16.5% vs 41.9% (P=0.0351) Distress (no/yes), medication prescriptions 94.3% vs 99.3% (P=0.0135) Significant among colorectal cancer Distress (no/yes), dental visits 47.8% vs 12.2% (P=0.0025) Not significant among mixed cancer Distress and office-based visits Not significant among breast cancer Distress and office-based visits, hospital outpatient visits, home healthcare visits and medication prescriptions Not significant among prostate cancer Distress and hospital outpatient visits, inpatient visits, home healthcare visits and dental visits Not significant among colorectal Distress and hospital outpatient visits, inpatient visits, home healthcare visits emergency visits and medication prescription

^a Article is also presented in table 1b, 1c or 1d.
^b Significant results in this column indicate a positive association between psychological problems and healthcare use, unless otherwise specified.
^c Abbreviations: CBMTG, Canadian Blood and Marrow Transplant group; Diff, difference; DT, distress thermometer; ED, emergency department; ER, emergency room, FCR, fear of cancer recurrence, FCRI, Fear of Cancer Recurrence Inventory; GAD, Generalized anxiety disorder; GAD-7, Generalized anxiety disorder-7; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HHC, hepatocellular carcinoma; ICD-9-CM, International Classification of Diseases; ICU, intensive care; IRR, incidence rate ratios, K6, Kessler-6; OR, Odds ratio, PHQ, Patient Health Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; PR, prevalence ratio; SCID, Structured Clinical Interview for DSM-IV; TIC-P, The Trimbos/iMTA questionnaire for Costs associated with Psychiatric illnesses

Table 1b. Overview of articles which included psychological problems in relation to **economic losses by patients and family.** (*this table is shown over two pages*)

First author, year, Study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Losses of patients and family	Measurement healthcare use	Results ^b
Champagne, 2018, Canada ^a	Longitudinal (follow-up at 0, 2, 10, 14 and 18 months)	Mixed cancers (955)	+ age between 18 and 80 + first cancer diagnosis non metastatic to be scheduled to receive a surgery - severe psychiatric disorder - diagnosed or treated for sleeping disorder	FCR FCRI-SF ((≥ 13))	CAM: homeopath/osteopath, massage therapist, chiropractor, acupuncturist, and other	Study-specific questionnaire	Not significant FCR and CAM ($F=1.25$, $P=0.264$)
Thewes, 2012, Australia ^a	Cross-sectional	Early breast cancer (218)	+ age between 18 and 45 + early breast cancer (stage0-2) + diagnosed at least 1 year ago + completed hospital based treatment, no history of recurrent disease or new primary cancer + 50 months (mean) after diagnosis	FCR FCRI (severity subscale >13) (subsca ^a $\leq 0-36$)	CAM: professional counselling, massage, physiotherapy, lymphoedema therapy, chiropractics, medications for anxiety, or depression, medication for sexual dysfunction, naturopathy, herbs, homeopathy, Reiki, acupuncture, meditation, yoga, hydrotherapy, hypnosis, Chinese medicine, reflexology, prayer or spiritual healing.	Self-report over the past 12 months	Significant FCR and number of CAM used (1.8 ($0.2-3.5$)) ($P=0.03$) Not significant FCR and CAM use (yes/no)
Manne, 2015, USA	Cross-sectional	Early stage breast cancer (143 patients and spouses)	+ patients had breast cancer surgery + 18 years or older + spouses worked for the past month	Cancer specific distress (Impact of Event Scale)	Healthcare use by spouses: Visits of different types of physicians in the past year (e.g., internist, cardiologist, urologist, radiologist, surgeon, oncologist, and neurologist) Losses of work productivity and absenteeism of the spouses	HPQ, questionnaire	Significant patient cancer distress and healthcare use spouses (correlation= -0.23) (<0.05) (negative) Patient cancer distress and losses of work productivity of spouses (correlation= 0.18) ($P<0.05$) Patient cancer distress and spouses absenteeism (correlation= 0.18) ($P<0.05$)
Compen, 2018, Netherlands ^a	Cross-sectional	Mixed cancers (245)	+ HADS ≥ 11 + stable 3 months psychotropic medication + current active anticancer treatment - severe psychiatric morbidity - previous mindfulness intervention	Anxiety, depression and adjustment disorder Psychological distress HADS, SCID-I	CAM: homeopaths, acupuncturists, traditional Chinese medicine, and massage therapists.	TiC-P	Significant Distress and complementary healthcare (IRR= 1.03 ($1.00-1.06$)) ($P<0.05$) Anxiety symptoms and complementary healthcare (IRR= 1.06 ($1.01-1.11$)) ($P<0.05$) Not significant Depression, anxiety and adjustment disorder and depressive symptoms with complementary healthcare use.
Litzelman, 2020, US	Cross-sectional	Spouses of mixed cancer patients (1882) and mixed cancer patients (1882)	- nonmelanoma skin cancer - patients with missing data - if spousal reported cancer diagnosis	Distress, depressive mood K6 ($(\geq 3$ 5), PHQ-2 (≥ 3) >5)	Mental healthcare use of spouses (antidepressant, antianxiety medication, psychotherapy visit) (any/none)	Medical Expenditure Panel Survey (MEPS)	Significant Elevated depressed mood and mental healthcare use spouses (OR= 0.59 ($0.36-0.96$)) (negative) Not significant Elevated distress and mental healthcare use spouses
Sarker, 2015, Germany	Cross-sectional	Mixed cancers (335)	+ 18 years or older + a malignant tumor (all tumor entities and disease stages) + 12 ($21.3-228$) (mean, SD range) months after cancer diagnosis, - presence of psychical, psychological and/or cognitive impairments	FCR and anxiety FoP-Q-SF (high FCR >34), GAD-7 (categorical)	CAM (yes/no)	Self-report over one year	Not significant FCR and CAM use

^a Article is also presented in table 1a, 1c or 1d.
^b Significant results in this column indicate a positive association between psychological problems and losses of patients and family, unless otherwise specified.
^c Abbreviations: CAM, complementary and alternatively medicine; FCR, fear of cancer recurrence, FCRI, Fear of Cancer Recurrence Inventory; IRR, incidence rate ratios, TIC-P, The Trimbos/iMTA questionnaire for Costs associated with Psychiatric illnesses

Table 1b. Continued

Table 1c. Overview of articles which included psychological problems in relation to **economic losses in other sectors** (*this table is shown over two pages*)

First author, year	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome	Work productivity	Measurement instrument work productivity	Results ^a
Den Bakker, 2019, Netherlands	Cross-sectional (retrospective registry based cohort)	Colorectal cancer (317)	+ 18 years or older + treated with curative intent - diagnosis of recurrent colorectal cancer - another cancer diagnosis during sick leave	Emotional distress	RTW (1 and 2 years after diagnosis)	Study specific questionnaire	Significant Distress and RTW after 1 year (OR=0.47 (0.25-0.89)) (P=0.020) Distress and RTW after 2 years (OR=0.39 (0.22-0.67)) (P=0.001)
Dumas, 2020, France	Prospective cohort (baseline at diagnosis, 3-6 months after treatment and 2 years after diagnosis)	Breast cancer (1874)	+ diagnosed stage I-III + younger than 57 years - history of cancer within the past 5 years - women without information about work situation - not employed at diagnosis - not treated with curative intent	Anxiety and depression HADS (non-case: 0-7, doubtful case: 8-10, case: 11-21)	RTW (2 years after diagnosis)	Study specific question	Significant/not significant Depression (case/non case) and RTW (OR= 2.29 (1.34-3.91)) Anxiety (case/non case) and RTW (OR= 1.47 (1.02-2.11)) Anxiety (doubtful case/non case) and RTW (OR = 1.71 (1.26-2.32)) Not significant Depression (doubtful/case-non case) and RTW
Horsboel, 2015, Denmark	Longitudinal (1 year follow up)	Hematological malignancy (105)	+ age between 19 and 59 + 6 to 9 months diagnosed prior to inclusion + employed at inclusion	Anxiety and depressive symptoms HADS (>8 and > 11)	RTW (1 year after diagnosis and long sickness absence)	Register for Evaluation of Marginalization (DREAM).	Not significant Anxiety and depression and RTW
Landeiro, 2018, Brazil	Longitudinal (6, 12, 24 months after diagnosis)	Breast cancer (121)	+ age between 18 and 57 + <5 months post diagnosis + employed at diagnosis - pregnancy - a previous cancer diagnosis - not insured	Depression	RTW (2 years after diagnosis)	Study specific questionnaire	Significant Depression and reduced RTW (OR=0.07 (0.01-0.63)) (P=0.017)
Rosbjerg, 2020, Denmark	Longitudinal (followed 15 months after baseline)	Mixed cancer (114)	+ age between 18 and 62 + all treatment intentions + initiating chemotherapy last 24 months + employed at time of diagnosis + time since diagnosis (69,5 days (mean))	Depression Back's Depression Inventory (no depression (0-13), moderate depression (20-28), severe depression (29-63))	RTW (follow-up till 15 months after baseline)	DREAM database	Significant Symptoms of depression and RTW (HR=0.58 (0.32-1.07)) (P=0.082)
Schmidt, 2019, Germany	Retrospective study	Breast cancer (135)	+ completed the 5-year follow-up after surgery + been employed at time of diagnosis - patients who were during follow-up no longer disease free or not at working age (≥65)	Depressive symptoms CES-D	Impaired RTW (1 and 5 years after breast surgery)	Study specific questionnaire	Significant Depressive symptoms at end of surgery and RTW 1 year after surgery (OR=2.9 (1.1-8.0)) Not significant Depressive symptoms 1.5 year after surgery and RTW 5 years after surgery
Schonfield, 1972, USA	Longitudinal	Mixed cancer (42)	+ good or excellent prognosis for 5 year survival + fulltime working before diagnosis - no malignancies	Anxiety levels IPAT anxiety scale questionnaire	RTW (9 months after first interview)	Interview	Significant Anxiety (higher) and RTW (P=0.02), anxiety score: working 20.2 VS not working 28.8
Spelten, 2003, Netherlands	Longitudinal	Mixed cancers (214)	+ age between 18 and 60 + treatment with curative intent + paid employment at time of diagnosis + within 4-6 months following their first day of sick leave	Depression CES-D	RTW (6, 12 and 18 months after first sick leave)	Self-report	Significant Depression quartiles and RTW (HR=0.81 (0.66–0.99))

^a Significant results in this column indicate a positive association between psychological problems and losses of patients and family, unless otherwise specified.
^b Abbreviations: HADS, Hospital Anxiety and Depression Scale; ICD-9-CM, International Classification of Diseases; ICU, K6, Kessler-6; SCID, Structured Clinical Interview for DSM-IV; CES-D, Center for Epidemiologic Studies Depression Scale; ICD-9-CM, International Classification of Diseases; K6, Kessler-6; RTW, return to work.** Significant results in this column indicate a negative association between psychological problems and return-to-work, unless otherwise specified.

Table 1c. Continued

Table 1d. Overview of articles which included psychological problems in relation to **costs in monetary units** (*this table is shown over two pages*)

First author, year, Study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)
Compen, 2018, Netherlands ^a	Cross-sectional	Mixed cancers (245)	+ HADS ≥ 11 + stable 3 months psychotropic medication - severe psychiatric morbidity - previous mindfulness intervention	Anxiety, depression and adjustment disorder Psychological distress SCID-I, HADS
Gu, 2020, United States	Retrospective cohort study	Mixed cancer (breast, lung, prostate) (710)	+ at least one inpatient and two outpatient claims or medical provider claim - patients lost with follow-up	Depression Study specific questionnaire (yes/no)
Pan, 2015, USA ^a	Cross-sectional	Mixed cancer patients (4766)	+ older than 21 years + reported with cancer in 2006-2009	Depression Medical record (ICD-9-CM)
Mausbach, 2018, California ^a	Cross-sectional	Mixed cancer patients (13 233)	+ 18 years or older + at least one health care claim within 1 year of the cancer diagnosis	Depression Medical record (ICD-9-CM)
Mausbach, 2020, California ^a	Retrospective cohort	Mixed cancers (13426)	+ diagnosis of cancer in 2014 + 18 years or older + at least one healthcare claim within 1 year of cancer diagnosis	Anxiety, Depression Medical record (ICD-9-CM)

Table 1d. Continued

Healthcare costs categories	Measurement healthcare use and cost valuation	Results ^b
<i>mental health</i> care including visits to social workers, psychologists, and psychiatrists. <i>Primary health care</i> including visits to GP, occupational physicians, and physical and occupational therapists. <i>Somatic health care</i> including visits to medical outpatient clinics, ED, day health care units, and overnight hospital stays, prescription medication costs. <i>Complementary health care</i> utilization including visits to homeopaths, acupuncturists, traditional Chinese medicine, and massage therapists.	Trimbos/iMTA questionnaire for Costs associated with Psychiatric illnesses (TiC-P), calculated into costs using Dutch reference prices	Significant Depression disorder and mental healthcare (OR=3.44 (1.56-7.12)) Anxiety disorder and mental healthcare (OR= 3.92 (1.58-9.73)) Distress and mental healthcare (OR= 1.09 (1.04-1.14)) (B=1.04 (1.01-1.07)) Depressive symptoms and mental healthcare (OR= 1.16 (1.07-1.25)) Anxiety symptoms and mental healthcare (OR= 1.11 (1.03-1.20)) (B= 1.11 (1.05-1.16)) Not significant Depression disorder, anxiety disorder, adjustment disorder, distress, anxiety symptoms and depressive symptoms with primary, somatic and complementary healthcare. Depressive disorder, anxiety disorder, adjustment disorder and depressive symptoms with mental health care
Healthcare expenditures (medicine, dental, home health, hospice inpatient, nursing facilities, outpatient)	Over 24 months since year of diagnosis) Medi-care Current Beneficiary Survey (MCBS)-Medicare sponsored by the Centers for Medicare & Medicaid Services (index year 2017)	Significant Depression (yes/no) and medical provider (B=0.38 (0.1)) (change \$ = 11,454 (4472-19,729) (P<0.001) Depression (yes/no) and inpatient (AOR=2.94 (1.82-4.74)) (change \$ = 8213 (3477-13,998) (P<0.001) Depression (yes/no) and other (B=0.41 (0.16) (change \$ = 405 (69-870) (P<0.05) Depression (yes/no) and Medicare (B=0.37 (0.01) (change \$ = 8280 (3570-13,977) (P<0.001) Depression (yes/no) and out of pocket (B=0.28 (0.13) (change \$ = 1270 (139-2720) (.01≤P< .05) Not significant Depression and hospital outpatient and prescribed medicine
Inpatient and outpatient care, emergency department visits, prescriptions, home health care, durable medical equipment, dental care, eye care, and others types of health care (1 year)	The sum of all direct actual third-party payments made to the providers for services rendered plus the out-of-pocket spending by the individual or family (index year 2009)	Significant Depression and total costs (B=9.136) (P<0.001) Depression and outpatient costs (B=8.468) (P<0.001) Depression and prescription costs (P<0.001)
Annual outpatient (ambulatory) office visits, ED visits, hospital visits, and mental health visits	Electronic medical records	Significant Depression (yes/no) and total charges (\$235,337 (SD=\$8573) vs \$110,650 (SD= \$1699)) (B=2.13) (P<0.05) Depression (yes/no) and outpatient costs (\$175,284 (SD=\$6781) vs \$87,024 (SD=\$1413)) (B=2.01) (<0.05) Depression and ED costs (\$11,154 (SD= \$359) vs \$8152 (SD=\$170)) (B=1.37) (P<0.05) Depression and inpatient costs (\$188 895 (SD=\$6251) vs \$128 272 (SD=\$2512)) (B=1.47) (P<0.05)
Healthcare costs (total annual healthcare charges, annual outpatient (ambulatory) office charges, ED charges, and inpatient hospital charges)	Provided by the UC San Diego Health cost-accounting system (electronic records)	Significant Depression and total charges (B=1.38 (125-1.52)) (P<0.001) Depression and ambulatory charges (B=1.44 (1.35-1.52)) (P=0.001) Depression and ED charges (B=1.26 (1.13-1.40) (P<0.001) Depression and inpatient hospital charges (B=1.21 (1.09-1.35) (P<0.001) Anxiety and total charges (B=1.77 (1.61-1.94)) (P<0.001) Anxiety and ambulatory charges (B=1.54 (1.46-1.64)) (P<0.001) Anxiety and total charges (B=1.29 (1.16-1.44) (P<0.001) Anxiety and inpatient hospital charges (B=1.31 (1.18-1.46) (P<0.001)

Table 1d. Continued

First author, year, Study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)
Boele, 2020, Netherlands	Longitudinal (6, 12, 18, 24 weeks and 6 and 12 months follow-up)	Glioma patients (90)	+ 18 years or older + glioma patients with I, II, III stage + CES-D score>=12 + 3.4 years (mean) time since diagnosis - suicidal intent	Depression CES-D
Fox, 2013, USA ^a	Retrospective	Breast cancer (40,202)	+ 18 years or older + procedure for mastectomy - breast conserving surgery	Psychiatric disorder (i.e. major depression, GAD, adjustment disorder, panic disorder) Medical record (ICD-9)
Jayadevappa, 2012, USA ^a	Longitudinal (1 year prior to diagnosis, and 5 year post diagnosis	Prostate cancer (50,147)	+ older than 66 years	Depression Medical record (ICD-9)
Jeffery, 2019, USA ^a	Cross-sectional (Retrospective)	Head and neck cancer (2944)	+ age between 18 and 64 + the rank of the military sponsor was enlisted or officer + healthcare was delivered within US	Anxiety, depression and adjustment disorder Military data repository (ICD-9) (yes/no)
Jeffery, 2012, USA ^a	Cross-sectional	Mixed cancers (11014)	+ at least 1 healthcare service record in fiscal year 2006 + 18 years or older + survived at least 2 years after their initial cancer treatment - nonmelanoma skin cancer	Depression Medical record (ICD-9)
Lee, 2018, Taiwan ^a	Population-based cohort study retrospectively	Hepatocellular carcinoma (223 matched with non-disorder (anxiety and depression) group)	+ treated between 1996 and 2010 + 18 years or older + history of HHC enrolment in registry for catastrophic illness patient database - patient with anxiety or depression before diagnosis	Anxiety and depression Medical record (ICD-9)
Niazi, 2018, USA ^a	Cross-sectional	Multiple myeloma (36,007)	+ diagnosed between 1991 and 2010 + full medical coverage	Depression Medical record (ICD-9)

Table 1d. Continued

Healthcare costs categories	Measurement healthcare use and cost valuation	Results ^b
Direct costs of healthcare utilization from appointments and medication (including oral chemotherapy, but excluding procedures such as surgery and/or radiotherapy), and indirect costs due to productivity loss in three modules: absence from paid employment; production loss without absence from paid employment; and impediments to paid or unpaid employment	Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P) including the Short-Form Health and Labor Questionnaire (SF-HLQ) (index year 2019)	Significant Depression and healthcare utilization costs (+€24,459 (3,662-42,250) per four weeks with each unit increase in scores) (P=0.001) Not significant Depression and medication costs, overall costs and productivity loss costs
Total healthcare costs	NIS reports (electronic medical record), actual charges (index year 2008)	Significant psychiatric disorder and costs (P<0.001).
Direct medical costs: physicians and other health professionals, care provided in hospitals, outpatient and ER costs, inpatient medications and laboratory services costs	SEER-Medicare linked data (index year 2009)	Significant Treatment phase depression and costs year of diagnosis (OR=1.52 (1.39-1.66)) Post treatment depression and cost in year 4/5 post diagnosis (OR= 1.89 (1.78-2.00)) Not significant Post treatment depression and costs year of diagnosis Treatment phase depression and costs in cost in year 4/5 post diagnosis
Total annual reimbursed cost adjusted to 2014 dollars	Military data repository (index year 2014)	Significant Depression and total costs (B=0.30 (0.024-12.53)) (P<0.0001) Anxiety and total costs (B=0.26 (0.027-9.51)) (P<0.0001) Adjustment disorder and total costs (B=0.23 (0.036-6.21)) (P<0.0001)
Total costs	Total cost that were reimbursed or paid to the provider in fiscal year 2009. Costs incurred by the patient or covered by other health insurance were not included.	Significant Depression yes/no and mean costs per provider (7,728 (13,104) vs. 16,212 (30,874)) (P<0.05)
outpatient costs, inpatient costs, inpatient costs and total treatment costs (1 and 5 years after diagnosis)	Administrative claims for reimbursement from the Taiwan Bureau of National Health insurance	Significant Year 1 after diagnosis costs Anxiety/depression and inpatient cost (diff.=1251) Anxiety/depression and outpatient cost (diff.=1665) Anxiety/depression and treatment cost (diff.=2969) Year 5 after diagnosis costs Anxiety/depression and inpatient cost (diff.=2079) Anxiety/depression and outpatient cost (diff.=3345) Anxiety/depression and treatment cost (diff.=5303)
Total healthcare costs (within the first 6 months after the diagnosis)	SEER-medicare (index year 2013)	All P values are <0.001 Significant Depression and total costs (OR= 1.23 (1.16-1.30)) and inpatient costs (OR= 1.33 (1.24- 1.42)) all P<0.001. Not significant: depression and outpatient costs

Table 1d. Continued

First author, year, Study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)
Han, 2015, US ^a	Cross-sectional	Mixed cancers (3309)	+ history with cancer + older than 18 years - non melanoma skin cancer	Psychological distress K6 (≥13)

^a Article is also presented in table 1a, 1b or 1c.
^b Significant results in this column indicate a positive association between psychological problems and costs, unless otherwise specified.
^c Abbreviations: Diff, difference; ED, emergency department; ER, emergency room, FCR, GAD, generalized anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HHC, Hepatocellular carcinoma, CES-D, Center for Epidemiologic Studies Depression Scale; ICD-9-CM, International Classification of Diseases; K6, Kessler-6; SCID, Structured Clinical Interview for DSM-IV

Table 1d. Continued

Healthcare costs categories	Measurement healthcare use and cost valuation	Results ^b
Medical provider visits, hospital outpatient visits, inpatient discharges, emergency department visits, dental visits, prescribed medicines and total expenditures	Survey and contacting medical providers	Significant in mixed cancers Distress (no/yes), hospital outpatient costs 35.0% vs 43.3% (P=0.0013) Distress (no/yes), hospital inpatient costs 15.9% vs 27.2% (P=0.0006) Distress (no/yes), emergency costs 16.3% vs 33.9% (P<0.0001) Distress (no/yes), dental visit costs 52.0 vs 26.8 (P<0.0001) (negative) Distress (no/yes), home healthcare costs 5.5 vs 16.5 (P<0.0001) Distress (no/yes, medicine prescriptions costs 90.6 vs 95.5 (P=0.0011) Significant in prostate cancer Distress (no/yes), office based costs 95.7% vs 99.3% (P=0.0195) Distress (no/yes), emergency costs 15.9% vs 41.9% (P=0.0322) Distress (no/yes), medication prescriptions costs 94.3% vs 99.3% (P=0.0135) Significant in colorectal cancer Distress (no/yes), dental visits costs 46.5% vs 12.2% (P=0.0032) Significant in breast cancer Distress (no/yes), hospital inpatient costs 11.7% vs 27.0% (P=0.0184) Distress (no/yes), emergency costs 13.4% vs 29.4% (P=0.0131) Distress (no/yes), dental visits costs 59.6% vs 38.0% (P=0.0099) Not significant in mixed cancer Distress and office-based costs, total expenditures and total costs Not significant in prostate cancer Distress and hospital outpatient, inpatient, home healthcare and dental Not significant in colorectal cancer Distress and hospital outpatient, inpatient, home healthcare emergency, medication prescription and total costs Not significant in breast cancer Distress and office-based costs, hospital outpatient, home healthcare, medication prescriptions and total costs

In summary, all studies were published between 1972 and 2020, of which 24 studies^{24, 26-30, 32, 35-37, 43, 48-50, 53, 55-57, 60, 62, 63, 65, 67, 70, 71} were published after December 2017. Most of the studies were conducted in the United States (N=27)^{27, 34-38, 41-44, 46, 50, 52-61, 66, 70-72}, Netherlands (N=8)^{26, 29, 30, 39, 45, 67, 68}, Germany (N=3)^{33, 64, 65} and Canada (N=3)^{28, 47, 51}. Studies were most often performed among mixed cancer patients (N=20)^{27-29, 33, 36-38, 41, 44, 47, 50, 53, 54, 61-64, 66, 68, 70} and breast cancer patients (N=11)^{32, 34, 38, 45, 49, 52, 59, 60, 63, 65, 71}. Other studies were performed across a variety of other cancer patients: colorectal (N=5)^{25, 30, 38, 39, 67} prostate cancer (N=2)^{38, 42}, lung cancer (N=3)^{55, 56, 72}, hepatocellular carcinoma (N=2)^{48, 57}, head and neck cancer (N=2)^{43, 46}, Gynecologic cancer (N=1)³¹, glioma cancer (N=1)²⁶, gastrointestinal cancer (N=1)³⁵, hematological malignancy (N=1)⁴⁰ and lymphoma (N=1)²⁴ patients. Sample sizes ranged from 42 to 50,147 patients.

Of all 49 studies, 34 studies^{24, 26-28, 30-33, 35-40, 45, 47, 49-52, 58-60, 62-69, 71, 72} focused on psychological symptoms, 14 studies^{25, 34, 41-44, 46, 48, 53-57, 61} focused on a psychiatric disorders and 1 study²⁹ on both. Focusing on psychological symptoms, 10 studies^{31-33, 39, 40, 45, 58, 64, 66, 72} investigated symptoms of anxiety as measured using the Hospital Anxiety and Depression Scale (HADS), General Anxiety Disorder-7 (GAD-7), State-Trait Anxiety Inventory (STAI) or PROMIS Anxiety or Patient Health Questionnaire-4 (PHQ-4), 20 studies^{26, 27, 29, 32, 33, 35, 36, 39, 40, 45, 49-51, 58, 59, 63, 65, 67, 70, 72} investigated symptoms of depression as measured using the HADS, PHQ-9, Center for Epidemiological Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), PROMIS, Back Depression Inventory II or a study specific questionnaire, 6 studies^{28, 47, 52, 60, 64, 69, 71} investigated fear of cancer recurrence measured with the Fear of Cancer Recurrence Inventory – Short Form (FCRI-SF), Concerns About Recurrence Scale (CARS) or the Fear of Progression Questionnaire - Short Form (FoP-Q-SF), and 11 studies^{24, 30, 33, 37, 38, 50, 52, 58, 62, 67, 70} investigated distress measured with the HADS, Impact of Event Scale, Distress Thermometer or Kessler Psychological Distress Scale (K10 and K6).

Of the 14 studies^{25, 34, 41-44, 46, 48, 53-57, 61} that investigated psychiatric disorders one study used a psychiatric interview (i.e. The Structured Clinical Interview) to investigate the presence of a depression disorder. In all other studies, the psychiatric disorder was retrieved from medical files: two studies^{29, 43} focused on adjustment disorder, three studies^{29, 43, 53} on anxiety disorder, 13 studies^{25, 29, 41-44, 46, 53-57, 61} on depression disorder, and two^{34, 48} on presence of any psychiatric disorders (i.e. a combination of anxiety disorder and/or depression disorder and/or adjustment disorder).

Quality assessment

Thirty-seven of the 49 studies were of high methodological quality as demonstrated in Appendix B. Most of the studies (19/25) scored negative on the item 'patients who want to participate in study (participation rate)' due to a participation rate lower than 80%, a missing baseline participating rate or a selective non-response. Half of the

included articles (25/49) did not meet the criteria for sufficient reporting of baseline descriptives, in particular, time since diagnosis, tumor stage, and/or treatment were often not reported. Almost all studies (42/49) used multivariate analyses and included more than 100 patients (47/49).

Psychological problems in relation to healthcare use

Table 2a provides an overview of the results regarding type of psychological problem (i.e. anxiety symptoms, depressive symptoms, distress, fear of cancer recurrence, anxiety disorder, depression disorder, adjustment disorder or any psychiatric disorder) and type of healthcare use (i.e. mental, supportive non-mental, , primary, oncology-related, inpatient, outpatient, and medicine and other healthcare use). Thirty six studies^{24, 25, 27-29, 31, 33-35, 37-39, 41-48, 51, 53, 54, 56-62, 64, 67, 69-72} investigated 48 associations in total of which six showed a strong evidence two a moderate evidence and 40 showed inconclusive evidence.

We found strong evidence that a depression disorder was positively associated with increased mental healthcare use^{29, 41}. Also, there was strong evidence that fear of cancer recurrence was positively associated with more use of primary care (i.e. general practitioner^{60, 69}). In addition, strong evidence was found for a positive association between depression disorder and increased inpatient healthcare use (e.g. hospitalization, inpatient healthcare use and intensive care admission) as 9 studies^{25, 42-44, 46, 53, 54, 56} found a positive association and 3 studies^{46, 56, 61} found no association. The same holds for anxiety disorder and increased inpatient healthcare use^{43, 53}. Anxiety disorder^{43, 53} and depression^{25, 38, 42-44, 53, 54, 57} disorder were both found to be positively associated with increased outpatient care use (i.e. emergency department visits, ambulatory visits or general outpatient care use).

Moderate evidence (one high and one low-quality study)^{34, 48} was found for the association between any psychiatric disorder and inpatient care use (i.e. prolonged hospitalization or increased length of hospitalization). Moderate evidence was also found for the association between depression disorder and increased medication (i.e. number of prescriptions)^{25, 44}.

Inconclusive evidence was found for many (N=40) of the studied associations. Remarkable, however, were the negative associations found with regard to oncology related healthcare and psychological symptoms (i.e. depressive symptoms and fear of cancer recurrence) as these were the only examples of all healthcare use associations, in which studies demonstrated that the psychological symptoms were associated with decreased healthcare use (i.e. oncology-related visits , mammography screening and other screening practices)^{51, 69}.

Psychological problems in relation to economic losses by patients and family

Six studies^{28, 29, 50, 52, 64, 69} investigated in total 10 associations between psychological problems and economic losses by patients and family, namely use of CAM (N=4)^{28, 29, 64, 69}, healthcare use by spouses (N=2)^{50, 52} and lost work productivity of spouses (N=1)⁵² (Table 2b). Inconclusive evidence was found for all of the 10 investigated associations, of which eight due to the fact that only one study investigated the association. The association between fear of cancer recurrence and CAM use was investigated in three studies of which one study⁶⁹ found a positive association with increased number of CAM but no association with use of CAM (yes/no) among breast cancer patients, and two studies^{28, 64} found no association at all among a mixed cancer population.

Psychological problems in relation to losses in other sectors

Eight studies^{30,32,40,49,63,65,66,68} investigated in total three associations between psychological problems and losses in other sectors, all of them focused on return to work (Table 2c). Strong evidence was found that symptoms of anxiety and depression were negatively associated with return to work, indicating that patients with symptoms did not or returned later to work than patients without symptoms. Three studies found a negative association between anxiety symptoms and return to work at 9, 12 and 24 months after cancer diagnosis among mixed, breast and hematological cancer patients, respectively^{32,40,66}. Six studies found a negative association between depressive symptoms and return-to-work at 6, 12, 15, 18 and 24 months after diagnosis also among mixed, breast and hematological cancer patients^{32,40,49,63,65,68}. One study³² among breast cancer patients compared return-to-work among three groups of patients (no symptoms of depression, moderate symptoms of depression and severe symptoms of depression), which found that patients with severe symptoms of depression did return to work later than patients with low symptoms of depression, whereas no such difference was found in comparison to patients with moderate symptoms of depression. Inconclusive evidence was found on the association between distress and return-to-work among colorectal cancer patients⁶⁵.

Psychological problems in relation to losses in monetary units

Thirteen studies^{26, 29, 34, 36, 38, 42-44, 48, 53, 55, 57, 61} investigated 33 associations in total between psychological problems and costs in monetary units (i.e. mental, inpatient, outpatient medicine total healthcare, productivity losses and out of pocket costs) (Table 2d), of which four showed a strong association and 29 showed inconclusive evidence. There was strong evidence that a depression disorder was positively associated with inpatient, outpatient and total healthcare costs. Three high quality studies found a positive association between a depression disorder and inpatients costs among mixed cancer patients^{53,57,65}. Three high-quality studies^{53,55,61} also found a positive association between depression disorder and outpatient costs among mixed cancer patients, whereas one

high quality study⁵⁷ found no association among multiple myeloma patients. Six high-quality studies^{43, 44, 53, 55, 57, 61} found a positive association between a depression disorder and total healthcare costs among head and neck (N=1), multiple myeloma (N=1) and mixed (N=4) cancer patients. One additional study⁴² among prostate cancer patients reported a positive association between post-treatment depression disorder and total healthcare costs in year two and three following diagnosis, whereas no such association was found in the same study with total healthcare costs in the year following diagnosis or year four and five post diagnosis. Furthermore, there was strong evidence that an anxiety disorder was positively associated with total healthcare costs^{43,53} among mixed cancer patients. Inconclusive or limited evidence was found for all 29 other investigated associations.

Table2a. Psychological problems associated with healthcare use

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder ^a
Mental healthcare	N+	(1)(2)(3)	(4) ¹ (2)(3)	(5)(6)(3)	(7,8)	(3)		(9)(3)	
	N-								
	N0	(10)(11)(12)	(10)(4) ² (5)(1,11)	(10)(13)(14)	(15)(16)(12)				
	LoE	?	?	?	?	?		++	
Supportive non-mental healthcare	N+	(2)	(2)	(13)					
	N-								
	N0	(12)		(13)	(12)				
Primary care	LoE	?	?	?	?				
	N+		(4) ¹ (3)	(6)	(16)(8)				
	N-								
	N0	(1)(3)	(4) ² (1)	(3)		(3)	(3)	(17)(3)	
Oncology-related healthcare	LoE	?	?	?	++	?	?	?	
	N+	(2)	(2)		(16)(18) ²⁰				
	N-		(4) ²		(8)				
	N0		(4) ¹		(18) ²¹			(19)	
Inpatient	LoE	?	?		?			?	
	N+	(20) ⁵	(21)	(22)		(23)	(24)(23)	(25)(26)(24)(17)(27)(23)(19) ⁶ (28)(29) ¹²	(30)(31)
	N-								
	N0	(20) ² (32)	(33)(20)(34)	(35)(22)	(15)			(19) ⁸ (36)(29) ¹⁸	
Outpatient	LoE	?	?	?	?	?	++	++	+
	N+	(1)	(1)	(35) ³ (22)	(15)(7)	(23)	(24)(23)	(25)(26)(24)(36)(17)(27,28)(23)	(31)
	N-								
	N0		(34)	(35) ¹⁰ (22)	(15)(18)			(19)	
	LoE	?	?	?	?	?	++	++	?

Table2a. Continued

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder ^a
Medication	N+		(34)	(22)	(7) (16)			(25) (17)	
	N-								
	N0			(22)	(15)				
	LoE		?	?	?			+	
Other healthcare use	N+			(13) ¹² (22) ¹⁵	(16) ¹⁴				
	N-			(22) ¹⁹					
	N0	(3) ¹¹	(3) ¹¹	(3) ¹¹ (22) ¹⁶		(3) ¹¹	(3) ¹¹	(3) ¹¹ (36) ¹¹	
	LoE	?	?	?	?	?	?	?	

^a Combination of anxiety disorder and/or depression disorder and/or adjustment disorder
^b High quality studies were printed in bold and underlined
^c Abbreviations: N-, negative association, N+, positive association, N0, no association, LoE, level of evidence; +, moderate evidence positive associations; ++, strong evidence positive association; ?, inconclusive or limited evidence on association
^d 1.Healthcare use before depression diagnosis, 2. Healthcare use after depression diagnosis, 5. Readmission, 6. ICU admission, 7. Hospital length of stay, 8. Inpatient admission, 9. A little distress compared to never, 10. Sometimes and most times distress compared to never, 11. Somatic healthcare use, 12. Service use, 13. Other service use, 14. Phone calls 15. Home healthcare among mixed cancer patients, 16. Home healthcare among prostate, colorectal and breast cancer, 17. Men, 18. Women, 19. Dental healthcare among mixed and breast cancer patients, 20. Routine follow-up care cancer, 21. Healthcare provider visits related to cancer

Table 2b. Factors associated with economic losses by patients and family

		Psychological symptoms				Psychiatric disorders			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	
CAM	N+		(3)		(8) ¹				
	N-								
	N0		(12)	(3)	(7) (8) ² (12)	(3)	(3)	(3)	
	LoE	?	?	?	?	?	?	?	
Healthcare use of spouses	N+								
	N-		(37)	(38)					
	N0			(37)					
	LoE		?	?					
Lost work productivity of spouses	N+								
	N-								
	N0		(38)						
	LoE		?						

^a Abbreviations: N-, negative association, N+, positive association, N0, no association, LoE, level of evidence; ?, inconclusive or limited evidence on association, CAM, complementary and alternatively medicine use
^b High quality studies were printed in bold.
^c 1.Complementary and alternatively medicine use (number), 2. Complementary and alternatively medicine use (yes/no)

Table2c. Factors associated with economic losses in other sectors

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	
Return to work	N+								
	N-	(39) (40) (41)	(39) ¹ (40) (42)	(46)					
	N0		(43) (44) (45) ³						
	LoE	--	--	?					

^a Abbreviations: N-, negative association, N+, positive association, N0, no association, LoE, level of evidence; --, strong evidence negative association; ?, inconclusive or limited evidence on association;
^b High quality studies were printed in bold
^c 1. Depression case compared to non-case, 2. Depression doubtful case compared to non-case, 3. Return to work after 1 year, 4. Return to work after 5 years.

Table 2d. Factors associated with losses in monetary units

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder ^a
Mental healthcare	N+	(3)	(3) ¹	(3)			(3) ¹	(3) ¹	
	N-								
	N0		(3) ²				(3) ²	(3) ²	
	LoE	?	?	?			?	?	
Inpatient	N+		(47)	(22) ³			(24)	(48) (24) (28)	(31)
	N-								
	N0			(22) ⁴					
	LoE		?	?			?	++	?
Outpatient	N+		(47)	(22) ⁵			(24)	(36) (48) (24)	(31)
	N-								
	N0		(47)	(22) ⁶				(28)	
	LoE		?	?			?	++	?
Medication	N+			(22) ²				(36)	
	N-								
	N0		(47) (49)	(22) ⁸					
	LoF		?	?				?	
Total healthcare	N+		(49)			(23)	(24) (23)	(36) (48) (24) (27) ⁹ (23) (28) (25)	(30)
	N-								
	N0			(22)				(27) ⁹	
	LoE		?	?		?	++	++	?
Absenteeism/ presenteeism (costs)	N+		(49)						
	N-								
	N0		?						
	LoE								

Table 2d. Continued

		Psychological symptoms				Psychiatric disorder		
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder
								Any psychiatric disorder ^a
Out of pocket costs	N+		(47)					
	N-							
	N0							
	LoE		?					
Other costs	N+		(47)¹¹	(22)¹⁴				(31) ¹³
				(22)¹⁵				
	N-			(22)¹⁸				
	N0	(3)¹⁰	(3)¹⁰ (49)¹²	(3)¹⁰	(3)¹⁰	(3)¹⁰	(3)¹⁰	
				(22)¹⁶				
				(22)¹²				
LoE		?	?	?	?	?	?	?

^a Combination of anxiety disorder and/or depression disorder and/or adjustment disorder
^b Abbreviations: N-, negative association, N+, positive association, N0, no association, LoE, level of evidence; +, moderate evidence positive associations; ++, strong evidence positive association; ?, inconclusive or limited evidence on association;
^c High quality studies were printed in bold
^d 1. Measured with Odds ratio's, 2. Measured with Beta coefficients, 3. Among mixed and breast cancer patients, 4. Among prostate and colorectal cancer patients, 5. Among mixed cancers patients, 6. Among breast, prostate and colorectal patients, 7. Among mixed and prostate cancers, 8. Among breast and colorectal, 9. Year of costs taking into account differed, 10. Somatic and complementary healthcare costs, 11. Medicare and other costs, 12. Overall costs, 13. Treatment costs, 14. Home and dental care costs among mixed cancer patients, 15. Dental healthcare costs among colorectal and breast cancer patients, 16. Home healthcare costs among colorectal, prostate and breast cancer patients, 17. Dental healthcare costs among prostate cancer patients 18. Dental healthcare costs among mixed cancer patients.
^e (1) Keyzer-Dekker, (2) Holla, (3) Compen, (4) Lo, (5) Trevino, (6) Arts, (7) Champagne, (8) Thewes, (9) Jacobsen, (10) Faller, (11) Mosher, (12) Sarkar, (13) Hamilton, (14). Schuurhuizen, (15). Lebel, (16) Otto, (17) Bhattarai, (18) Vachon, (19) McDermott, (20) Nipp, (21) Oleske, (22). Han X, (23). Jeffery, 2019, (24) Mausbach, 2020, (25). Jeffery 2012, (26). Mausbach, 2017, (27) Jayadevappa, (28). Niazi, (29) Laurence, (30) Fox, (31) Lee, (32) Doll, (33) Cagle, (34). Godby, (35) Rana, (36) Pan X, (37). Litzelman, (38). Manne, (39) Dumas, (40) Horsboel, (41) Schonfield, (42) Landeiro, (43) Rosbjerg, (44) Spelten, (45). Schmidt, (46) Den Bakker, (47). Gu, (48) Mausbach 2018, (49) Boele

Discussion

The aim of this systematic review was to investigate associations between psychological problems and healthcare and societal related resource use and costs among cancer patients. In total 49 studies were included in this systematic review which investigated 94 different associations between psychological problems and healthcare or societal resource use or costs: 48 for healthcare use, 10 for economic losses of patients and their family, three on other losses such as return to work and 33 for total costs as measured in monetary units. For 14 of these 94 associations, moderate or strong evidence was found. Fear of cancer recurrence, having an anxiety disorder, having a depression disorder and having any psychiatric disorder were associated with higher healthcare use on at least one healthcare subcategory (i.e. mental, primary, inpatient or outpatient healthcare).

Anxiety symptoms and depression symptoms were associated with reduced return to work, presence of an anxiety disorder was associated with higher total healthcare costs; and presence of a depression disorder was associated with higher inpatient, outpatient and total healthcare costs. For all other 80 investigated associations inconclusive evidence was found, mostly due to limited studies or inconsistent evidence.

This study confirms the hypothesis made by Carlson and Bultz⁶ that cancer patients with psychological problems may not only have increased mental healthcare use but also make more use of other domains of healthcare. We found strong evidence that fear of cancer recurrence was positively associated with increased primary healthcare use. Inconclusive evidence was found for symptoms of anxiety, symptoms of depression, distress and fear of cancer recurrence in relation to all other healthcare use categories, often due to inconsistent findings. However, strong evidence was found that both anxiety disorder and depression disorder were associated with increased inpatient and outpatient healthcare use. In addition, evidence was found for an association between depression disorder and increased mental healthcare use and any type of psychiatric disorder (including anxiety and depression disorder) and inpatient care use. This discrepancy in findings between healthcare use and symptoms of anxiety and depression versus anxiety and depression disorder may be caused by a dose-response relationship; i.e. anxiety or depression problems may only result in higher healthcare use when the problem exceeds a certain threshold. However, it may also be that the association between symptoms of anxiety or depression and healthcare use only exists in certain groups of cancer patients or with specific healthcare use categories. This might explain why in a previous study among 4,020 mixed cancer patients no associations were found between anxiety and depressive symptoms and increased healthcare use³³, whereas in another study among 3,957 colorectal cancer patients this association was found to be significant³⁹.

In contrast to the hypothesis of Carlson and Bultz⁶, the only healthcare use category which showed, evidence (although inconclusive) of a negative association with psychological problems was oncology-related care. So far, five studies have investigated the association between symptoms of depression or fear of cancer recurrence and use of oncology related care of which two studies found lower oncology-related care use among patients with psychological symptoms^{39, 51, 69}. In four studies, however, also evidence was also found for no or a positive association ^{39, 51, 60, 71} (some studies found evidence for both a negative association and absence of an association). An explanation may be that patients with higher symptoms of depression or fear of cancer recurrence have a more avoidant coping style ⁷³ which may limit the uptake of specific types of oncology-related care. Further research is however needed to unravel this association.

With regard to economic losses of patient and family we found inconclusive evidence for all associations, mostly due to limited studies (i.e. eight of the 10 associations were investigated by only one study). Only two studies have investigated the association between psychological problems among breast cancer and mixed cancer patients and healthcare use and productivity losses among their spouses.

With regard to economic losses in other sectors, we found strong evidence that anxiety and depressive symptoms are negatively associated with return-to-work. These results are in line with the hypothesis of Carlson et al. that the economic consequences of psychological problems among cancer patients are larger than the economic costs of (mental) healthcare only⁶. In our systematic review, we only included articles which measured return-to-work with insight on time absent from work. Studies that investigated the association but without a clear timeframe for returning to work were excluded as the association between psychological problems and return-to-work in these studies may have been biased by time since diagnosis⁷⁴⁻⁷⁶. Remarkable, however, was that no study included in our systematic review investigated the association between psychiatric disorders and return-to-work. We hypothesize, however, that in line with the results on psychological symptoms and return-to-work, psychiatric disorders are also negatively associated with return to work.

With regard to losses in monetary units, strong evidence showed that depression disorder was positively associated with more inpatient care costs, outpatient care costs and total care costs. Anxiety disorder was also found to be positively associated with more inpatient care costs. Evidence on all other 26 associations was limited or inconclusive. Further research is needed to explore these associations and take possible moderators or mediators (e.g. coping style, social support) into account. For example, studies have demonstrated that cancer patients with psychological problems are more likely to develop comorbidities and are less likely to adhere to cancer treatment or lifestyle recommendations which may result in higher costs⁷. However, comorbidities may also lead to more psychological problems. The pathway via which psychological problems affect healthcare and societal resource use and costs, or the **reverse**, is thus not yet completely understood. Further research is needed on third variables such as coping style, and social support.

Study limitations

A strength of this study is that it focused on different psychological symptoms and disorders as well as different types of healthcare and societal costs. Also, in contrast to a previous systematic review¹³, the methodological quality of the included studies was investigated. Furthermore, we used the Dutch guidelines to define economic outcome categories. However, we acknowledge that this framework may not be suitable for all

countries, as in some countries, for example, the healthcare costs are paid directly by the patient (without insurance). In those countries healthcare resource use may need to be categorized as 'economic losses by patients and their family' instead of the category on 'healthcare use'. A limitation is that vote counting was used to summarize the findings of the included studies. The absence of an association in some of the included studies may have been the consequence of limited power rather than an actual absence of an association. Meta-analyses can solve this problem. However, we did not perform meta-analyses, as studies were very heterogeneous in study population, psychological problem, cost category investigated, as well as measurements instruments. Our aim was to provide an overview on all economic consequences investigated in relation to psychological problems among cancer patients and a summarized direction of an association instead of the magnitude of the association. Finally, a limitation of this study is that based on the included studies we cannot draw conclusions on the causality of psychological problems and healthcare, societal resource use and costs among cancer patients as almost all studies had a cross-sectional design.

Clinical implications

Results of this systematic review indicate that the economic consequences of psychological problems among cancer patients are beyond mental healthcare costs only. Psychological problems among cancer patients also impact societal costs such as losses due to delayed return to work. This information is important to consider when building a business case for the reimbursement of psychological treatment for cancer patients. Based on the results of this systematic review we claim that treating psychological problems in general among cancer patients may not only improve psychological well-being among cancer patients but also lead to medical cost offset and improved return-to-work. Two previous reviews^{77, 78} and later published studies⁷⁹⁻⁸¹ showed evidence that psychological treatment for patients with cancer is not only effective, but may also be cost saving. Several other studies are ongoing^{82, 83}, including one study on the effectiveness, cost-utility and budget impact of psychological treatment among cancer patients with an adjustment disorder⁸⁴, which, as also shown in this systematic review, is still an understudied population.

Conclusion

Psychological problems in cancer patients are associated with increased healthcare use, healthcare costs and economic losses, especially for (symptoms of) anxiety and depression disorder, and fear of cancer recurrence. Future research is needed on psychological problems in relation to understudied healthcare use or costs categories, productivity losses of patients and their caregivers, and informal care costs.

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Appendix

Appendix A and Appendix B are available online at <https://onlinelibrary.wiley.com/doi/full/10.1002/pon.5753>.

Chapter 3

The course of symptoms of anxiety and depression
from time of diagnosis up to 2 years follow-up in
head and neck cancer patients treated with primary
(chemo)radiation

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Summary

Purpose

To identify sociodemographic and clinical factors, health-related quality of life (HRQOL) and head and neck cancer (HNC) symptoms associated with the course of symptoms of anxiety and depression from pretreatment to 24-month follow-up among HNC patients after (chemo)radiation.

Methods

Patients (n=345) completed questionnaires on anxiety and depression (HADS), HRQOL and symptoms (EORTC QLQ-C30/QLQ-H&N35) before treatment, and 6-weeks, 3-, 6-12-, 18-, and 24-months after treatment. Mixed model analyses were used to investigate the course of anxiety and depression from pretreatment to 24-months in relation to factors assessed at baseline, and the course of anxiety and depression from 6- to 24-months, in relation to factors assessed at 6-months.

Results

Increased risk for anxiety (HADS-anxiety > 7) was 28.7% among patients before treatment, which declined to 10.0% at 24-months. Increased risk for depression (HADS-depression > 7) was 15.1% before treatment, 18.2% at 3-months, 7.2% at 12-months and 16.0% at 24-months. Factors assessed at baseline which were significantly associated with the course of anxiety were age, pain, problems with social contact, and feeling ill, whereas chemotherapy, worse emotional functioning, speech problems and weight loss were significantly associated with the course of depression. Regarding factors assessed at 6-months, chemotherapy, worse cognitive and social functioning, insomnia, swallowing problems and trouble with social eating were associated with the course of anxiety. Nausea/vomiting, dyspnea, coughing, and feeling ill were associated with the course of depression (p-values < 0.05).

Conclusions

Factors associated with a worse course of anxiety and depression are younger age, treatment with chemotherapy, worse HRQOL and higher symptom burden.

Background

Among head and neck cancer (HNC) patients, symptoms of anxiety are present in one third of the patients, and symptoms of depression are present in 15% to 50%¹⁻⁸. Symptoms of anxiety seem to stay stable over time from diagnosis up to 2 years after treatment⁹, while symptoms of depression seem to occur mostly during the first 6 months after diagnosis⁸.

Previous single studies have suggested that gender, age, tumor stage, and health-related quality of life (HRQOL) are associated with the course of anxiety. Research has shown that female HNC patients more often experience anxiety compared to men, and that anxiety is more common among younger patients and patients with a more advanced tumor stage^{2,3}. One study reported that patients with laryngeal cancer experienced the highest level of anxiety³, whereas another study found that patients with oral cancer experienced the highest². Neilson et al. (2013)⁹ found that treatment modality was not associated with anxiety, whereas Singer et al. (2012)¹⁰ did demonstrate that there was an association. Finally, three cross-sectional studies showed a significant association between anxiety and worse HRQOL, in particular with insomnia¹¹, poor general health and worse emotional functioning^{12,13}. Regarding the course of (symptoms of) depression, a recent systematic review showed that sociodemographic and clinical factors are likely not to be associated¹⁴. Findings on the association between the course of depression and HNC symptoms and HRQOL were inconclusive, although it seems that HNC symptoms such as speech and swallowing problems are associated with depression^{9,15,16}.

Limitations of previous studies include small sample sizes, low quality and/or no longitudinal study design. This study aimed to identify sociodemographic and clinical factors, and HRQOL and symptoms that might be associated with the course of symptoms of anxiety and depression (further called anxiety and depression) from baseline up to 2 years after treatment among HNC patients treated with primary (chemo)radiation. Also, we studied possible risk factors measured at 6-month follow-up for the follow-up course of anxiety and depression from 6- to 24-month follow-up. Based on the existing evidence, we hypothesized that the course of anxiety would be associated with sociodemographic and clinical factors as well as HRQOL and symptoms, whereas the course of depression would be associated with HRQOL and symptoms rather than sociodemographic and clinical factors.

The results of this study are relevant to identify HNC patients before, during, and shortly after treatment who are at risk for (developing) anxiety or depression in order to timely treat HNC patients with an increased level of anxiety or depression. It is additionally important to understand risk factors for the follow-up course of anxiety and depression

from 6- to 24-month follow-up, to identify those HNC patients who may need psychological care, after short term sequelae of HNC and its treatment have passed.

Method

Patients and procedure

Data of a prospective cohort study among newly-diagnosed HNC patients was used. Patients in this dataset were treated between January 2008 and June 2014 at Amsterdam UMC, location VUmc, Amsterdam, The Netherlands. Patients visiting the department of Otolaryngology-Head and Neck Surgery and radiotherapy, were asked to fill out patient-reported outcome measures (PROMs) using a touch-screen computer system called OncoQuest or using paper and pencil¹². This data collection was part of standard clinical care in which patients were screened for anxiety, depression and HRQOL at multiple time points: prior to treatment, 6-weeks after treatment and 3-, 6-, 12-, 18- and 24-months after treatment.

Patients were included in this study if 1) they were 18 years or older, 2) their treatment consisted of primary (chemo)radiation with curative intent for cancer of the oral cavity, oropharynx, hypopharynx, or larynx, 3) data regarding anxiety or depression (i.e., HADS) prior to the treatment was available and 4) they provided informed consent to use the collected data for research purposes. Consent procedures were approved by the Medical Ethical Committee of VUmc and followed the Dutch medical Research Involving Human Subjects Act.

Outcome measures

Patients were asked to fill out the Hospital Anxiety and Depression scale (HADS), EORTC QLQ-C30 and EORTC QLQ-H&N35 to measure anxiety and depression and HRQOL.

The HADS is a 14-item self-report questionnaire for measuring symptoms of anxiety (subscale HADS-A) and depression (subscale HADS-D) in patients with a somatic illness (e.g., cancer)¹⁷. Patients respond to all items on a 4-point Likert scale, resulting in a subscale score ranging from 0-21. A subscale score of >7 was used to identify patients with an increased risk for an anxiety or depression disorder.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQ-C30) contains a global health status/quality of life scale, five functioning scales, three symptom scales and six single items^{18,19}. The EORTC QLQ-H&N35 contains seven subscales and 11 single items on HNC symptoms specifically^{20,21}. Responses on the EORTC QLQ-C30 and EORTC QLQ-H&N35 are rated on

a 4-point Likert scale (1=not at all, 4=very much). The last five single items are rated on a yes/no scale and the items on global health status which range from 1 (very poor) to 7 (excellent). All scales and single-item scores are transformed into a score from 0 to 100. A high score on a functioning scale and the global health status scale corresponds with a higher (i.e., more positive) level of functioning, whereas a higher score on a symptom scale or single item represents a higher (i.e., more negative) level of problems.

All sociodemographic (age and gender) and clinical variables (tumor stage, tumor subsite and treatment modality) were assessed by medical record audit. Cancer treatment of patients consisted either of radiotherapy alone or a combination of chemotherapy and radiotherapy (chemoradiation).

Statistical analysis

Baseline characteristics were generated using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Differences between included and excluded patients were investigated using independent *t*-tests (for continuous variables) and chi-square tests (for categorical variables). To investigate the course of depression and anxiety over time, linear mixed models were used. A random intercept was applied for patient and fixed effects for measure. The prevalence of patients with an increased risk for an anxiety or depression disorder (HADS-A score >7 and HADS-D score >7) at each follow-up measure was also investigated.

To test whether sociodemographic and clinical factors and scores on the HADS and HRQOL questionnaires were associated with the course of anxiety and depression, multivariable linear mixed models were built. To investigate the course from pretreatment to 24-month follow-up, baseline sociodemographic, clinical, HADS and HRQOL factors were used. For the course from 6- to 24-month follow-up, factors as assessed at 6-month were used. All independent factors were included in the multivariable model using a forward selection procedure (*p*-entry 0.05). A random intercept was applied for patient and fixed effects were used for the outcome measure, independent variables and its two-way interaction (measure*independent variable). If the two-way interaction appeared to be significant (*p*<0.05), this was interpreted as a difference in the course of anxiety or depression for that specific variable. EORTC QLQ-C30 and EORTC QLQ-H&N35 scores were dichotomized using evidence based cut-off scores if available²² or mean scores of the general population (Appendix A)²³. Age was dichotomized using the median split (62 years). In case a group had less than 5 patients at one time point, this variable was excluded. In addition, variables which showed high correlation (i.e., >0.70) with other factors or the outcome measure were excluded from the analyses. All statistical analyses were conducted using SPSS 25.0.

Results

Patient characteristics

Of the 513 patients who were primary treated with (chemo)radiation during the study period, 171 patients did not fill in the PROMs or did not complete the HADS prior to the treatment, resulting in a study population of 345 patients. There were no significant differences between the included and excluded patients (Table 1).

Table 1. Characteristics of the participants and non-participants.

Characteristics	Participants n = 345	Non-participants n = 168	p-value
Mean age (SD)	61 (9.0)	62 (9.3)	0.53
Gender			
Male	251 (73%)	119 (71%)	0.65
Female	94 (27%)	49 (29%)	
Treatment			
Radiotherapy	185 (54%)	80 (48%)	0.20
Chemoradiation	160 (46%)	88 (52%)	
Tumor site			
Oral cavity	42 (12%)	21 (12%)	0.43
Oropharynx	156 (45%)	67 (40%)	
Hypopharynx	39 (11%)	27 (16%)	
Larynx	108 (31%)	53 (32%)	
Tumor stage*			
I	40 (12%)	15 (9%)	0.15
II	49 (14%)	25 (16%)	
III	87 (25%)	28 (17%)	
IV	168 (49%)	93 (58%)	

*Patients with an unknown TNM stage (included n = 1 ; excluded n = 7) were excluded from this analysis
abbreviations: SD, standard deviation

The majority of the study population was male (73%) and the mean age was 61 years (range 36-85). Most patients had a stage IV tumor (49%), followed by III (25%), II (14%) and I (12%). The tumor was most often located in the oropharynx (46%), followed by larynx (31%), oral cavity (12%) and hypopharynx (11%). About half of the patients (54%) were treated with radiotherapy and 46% were treated with chemoradiation. In total, 78% of all patients completed both the baseline questionnaire and at least one follow-up measure. Causes for dropout were not registered, except for death. In total 60 (17%) patients died during the 24-month follow-up period (Table 2).

The course of symptoms of anxiety and depression over time

The severity of symptoms of anxiety was highest before treatment (mean=5.78, SD=4.05), decreased at 6-weeks follow-up (mean=4.16, SD=3.65), and further

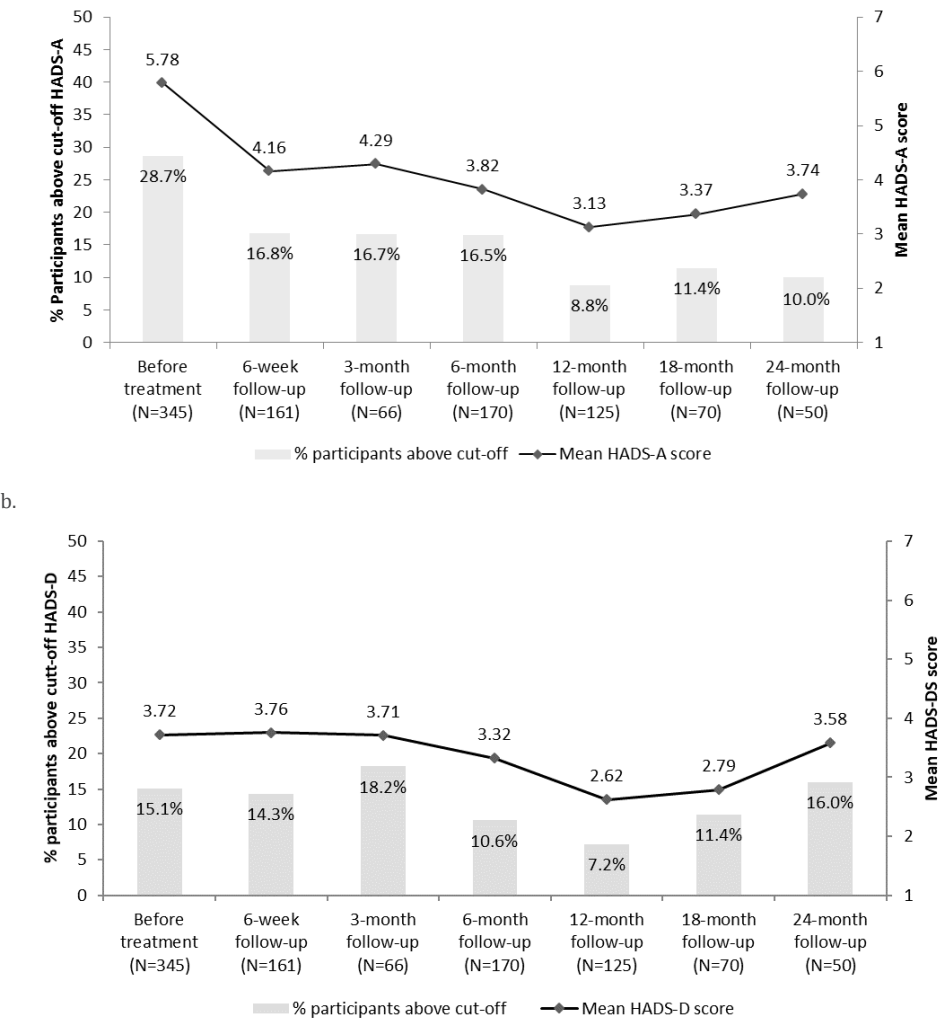
decreased up to 12-month follow-up (mean=3.13, SD=3.10) (Table 2, Figure 1a). From 12- to 24-month follow-up anxiety slightly increased again to a mean score of 3.74 (SD=3.57). Using a cut-off score of HADS-A > 7, 28.7% of the patients had an increased risk for an anxiety disorder before treatment, which decreased to 16.5% 6 months after treatment, and further decreased to 8.8%, 11.4%, and 10.0% at 12-, 18- and 24-month follow-up, respectively. The mean score for symptoms of depression was 3.72 (SD=3.72) at baseline (Table 2, Figure 1b) and remained almost stable up to 3-month follow-up. Thereafter, the mean score decreased until 12-month follow-up (mean=2.62, SD=3.07) and subsequently increased again up to 24-month follow-up (mean=3.58, SD=3.51. Pretreatment, 15.1% of the patients had an increased risk for a depressive disorder, and 14.3% and 18.2% 6 weeks and 3 months after treatment, which decreased to 10.6%, 7.2%, and 11.4% at 6-, 12- and 18-month follow-up and increased again to 16.0% at 24-month follow-up (Table 2, Figure 1b). Sensitivity analyses were carried out excluding patients who died during the 24-month follow-up period and a similar course of anxiety and depression was found compared to the entire group of patients (data not shown).

Table 2. Descriptive statistics and linear mixed model analysis on the course of symptoms of anxiety and depression

	n	Drop out due to death (n)	HADS score*		Increased risk**	Linear mixed model estimates	
			Mean (SD)	Median (IQR)	%	Mean change from pretreatment	95% CI
Anxiety (HADS-A)							
Pretreatment	345		5.78 (4.05)	5.00 (3.00-8.00)	28.7		
6-week post-treatment	161		4.16 (3.65)	3.00 (1.00-6.00)	16.8	-1.44	-1.95 ; -0.92
3-month post-treatment	66	2	4.29 (3.59)	3.50 (1.75-6.00)	16.7	-1.21	-1.96 ; -0.47
6-month follow-up	170	13	3.82 (3.65)	3.00 (1.00-6.00)	16.5	-1.73	-2.23 ; -1.23
12-month follow-up	125	24	3.13 (3.10)	3.00 (0.00-5.00)	8.8	-2.52	-3.09 ; -1.96
18-month follow-up	70	15	3.37 (3.17)	1.00 (3.00-5.00)	11.4	-2.48	-3.20 ; -1.76
24-month follow-up	50	6	3.74 (3.57)	3.00 (1.00-6.00)	10.0	-2.37	-3.20 ; -1.53
Depression (HADS-D)							
Pretreatment	345		3.72 (3.72)	3.00 (1.00-6.00)	15.1		
6-week post-treatment	161		3.76 (3.91)	2.00 (1.00-6.00)	14.3	0.45	-0.06; 0.96
3-month post-treatment	66	2	3.71 (3.51)	2.00 (1.00-6.25)	18.2	0.35	-0.38; 0.96
6-month follow-up	170	13	3.32 (3.47)	2.00 (1.00-5.00)	10.6	-0.06	-0.55; 0.44
12-month follow-up	125	24	2.62 (3.07)	1.00 (0.00-4.00)	7.2	-0.76	-1.32 ; -0.19
18-month follow-up	70	15	2.79 (2.97)	0.00 (2.00-4.25)	11.4	-0.54	-1.25 ; 0.18
24-month follow-up	50	6	3.58 (3.50)	1.00 (2.50-6.00)	16.0	-0.10	-0.94 ; 0.73

* A higher score indicates more symptoms of depression or anxiety
** Increased risk on a anxiety or depression disorder, based on a cut-off score of 7 for both HADS-A and HADS-D
***Patients who died, had tumor recurrence or a second primary tumor, or treatment or operation between measurements were detracted from the next assessments abbreviations: SD, standard deviation; CI, confidence interval

Figure 1. The course of anxiety and depression over time (pre-treatment to 24 month-follow-up). A higher score indicates more symptoms.



Factors associated with the course of symptoms of anxiety

Multivariable analysis showed that the course of anxiety from pretreatment to 24-month follow-up was significantly associated with age ($p=0.027$), pain ($p=0.011$), social contact ($p=0.006$) and feeling ill ($p=0.003$) (Table 3 and Figure 2). Younger patients had especially between 12- and 24-month follow-up a poorer course (i.e., scores got worse or improved less at a faster rate over time) of anxiety than older patients. Patients with pain reported more often higher mean scores of anxiety over time than patients who

reported no pain. Patients with problems with social contact reported more anxiety at baseline than patients without. This difference declined until 18-month follow-up, after which the difference increased again. Patients who felt ill reported more anxiety at baseline, and showed an improvement of anxiety over time, whereas patients who did not feel ill did not report a great difference in their anxiety over time. At 24-month follow-up, the level of anxiety was almost equal between the two groups.

Table 3. Results of univariable and multivariable analysis (forward selection procedure) regarding variables associated with the course of symptoms of anxiety and depression over time.

Variable ^a	Entire course from Pretreatment to 24-month follow-up (n=345)				Follow-up course from 6- to 24-month follow-up (n=170)			
	Anxiety		Depression		Anxiety		Depression	
	Uni P-value	Multi P-value	Uni P-value	Multi P-value	Uni P-value	Multi P-value	Uni P-value	Multi P-value
Demographic variables								
Time*gender	0.91		0.95		0.87		0.58	
Time*age	0.050	0.027	0.54		0.41		0.69	
Clinical variables								
Time*diagnosis	0.68		0.25		0.91		0.92	
Time*TNM stage	0.91		0.097		0.85		0.41	
Time*chemotherapy	0.53		0.023	0.009	0.20	0.019	0.93	
EORTC-QLQ-C30								
Time*Global quality of Life	0.15		0.035		0.079		0.42	
Time*Physical functioning	0.84		0.12		0.35		0.19	
Time*Role functioning	0.90		0.017		0.35		0.35	
Time*Emotional functioning	<0.001¹		0.029	0.011	0.058		0.076	
Time*Cognitive functioning	0.17		0.45		0.004	0.014	0.086	
Time*Social functioning	0.032		0.037		0.030	0.002	0.083	
Time*Fatigue	0.24		0.021		0.40		0.33	
Time*Nausea and vomiting	0.041		0.89		0.65		0.087	0.005
Time*Pain	0.22	0.011	0.21		0.33		0.82	
Time*Dyspnea	0.71		0.017		0.49		0.001	<0.001
Time*Insomnia	0.45		0.41		0.032	0.029	0.83	
Time*Appetite loss	0.050		0.31		0.015		0.041	
Time*Constipation	0.96		0.16		0.45		0.20	
Time*Diarrhea ²	N/A		N/A		N/A		N/A	
Time*Financial difficulties	1.00		0.036		0.85		0.341	
EORTC-QLQ-H&N35								
Time*Oral pain	0.90		0.31		0.38		0.54	
Time*Swallowing	0.66		0.76		1.00	0.007	0.75	
Time*Senses problems	0.79		0.59		0.94		0.39	
Time*Speech problems	0.02		0.009	0.034	0.73		0.24	
Time*Trouble with social eating	0.23		0.30		0.022	<0.001	0.041	
Time*Trouble with sexuality	0.68		0.44		0.11		0.093	
Time*Trouble with social contact	0.01	0.006	0.012		0.46		0.35	
Time*Teeth	0.79		0.41		0.31		0.94	
Time*Opening mouth	0.45		0.59		0.60		0.85	

Table 3. Continued

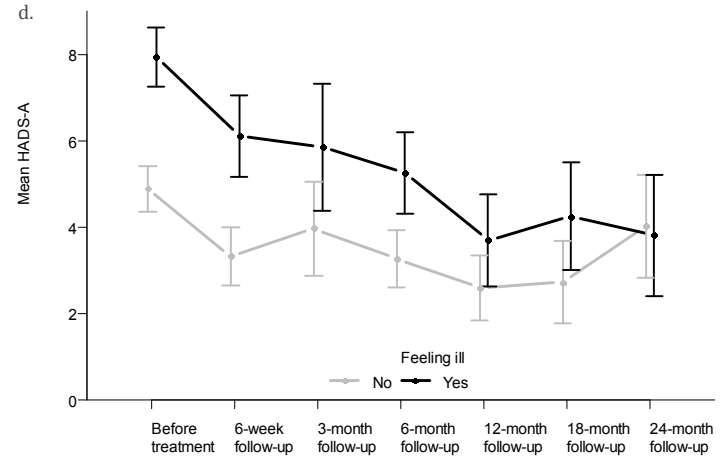
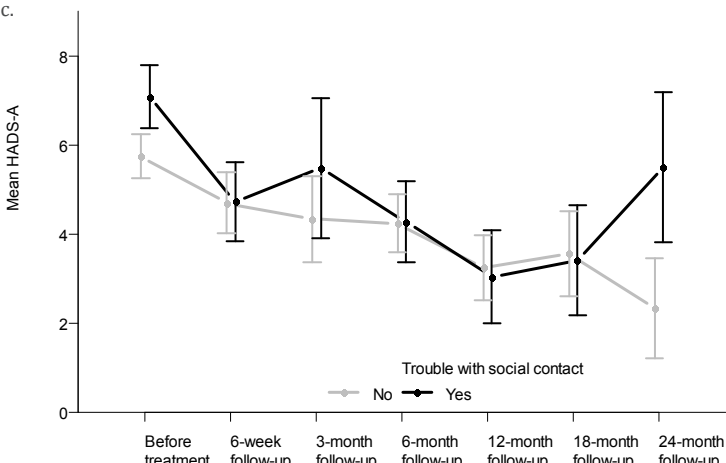
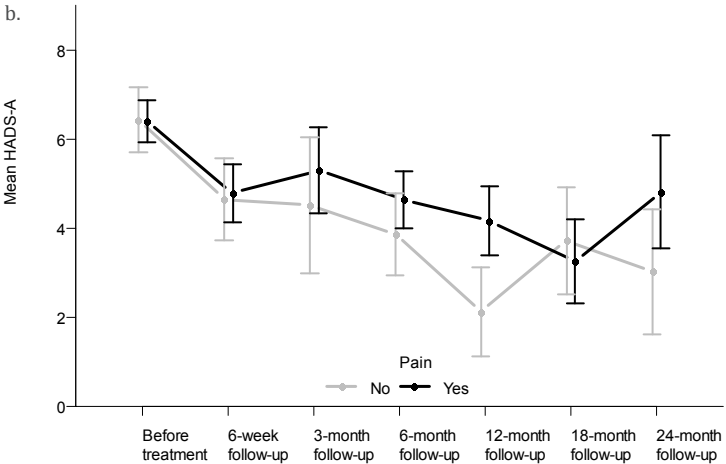
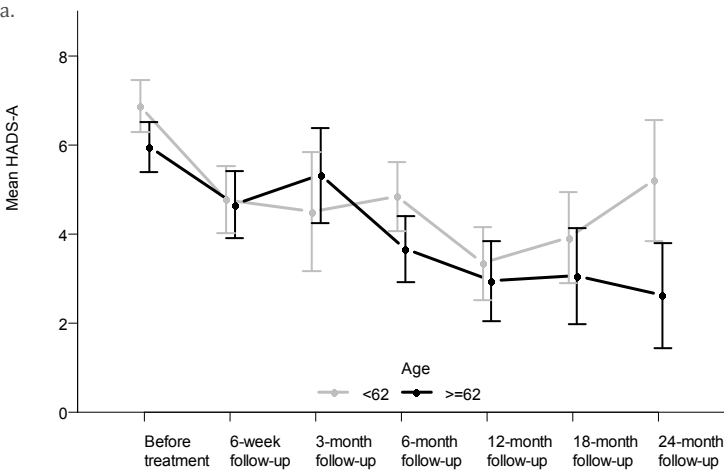
Variable ³	Entire course from Pretreatment to 24-month follow-up (n=345)				Follow-up course from 6- to 24-month follow-up (n=170)			
	Anxiety		Depression		Anxiety		Depression	
	Uni P-value	Multi P-value	Uni P-value	Multi P-value	Uni P-value	Multi P-value	Uni P-value	Multi P-value
Time*Dry mouth	0.44		0.49		0.73		0.36	
Time*Sticky saliva	0.58		0.34		0.72		0.20	
Time*Coughing	0.070		0.024		0.15		0.83	0.020
Time*Felt ill	0.013	0.003	0.15		0.014		0.005	0.003
Time*Use of painkillers	0.61		0.44		0.62		0.91	
Time*Nutritional supplements ²	N/A		N/A		N/A		N/A	
Time*Feedingtube ²	N/A		N/A		N/A		NA	
Time*Weight loss	0.36		0.007	0.006	0.69		0.42	
Time*Weight gain ²	N/A		N/A		N/A		N/A	

¹As expected the domain on Emotional Functioning was highly correlated with HADS-A ($\rho = -0.737$), therefore we excluded this variable from the analysis.

²These variables were excluded since they had less than 5 patients per groups at one or more time points. abbreviations: NA, not applicable

³“time*” indicates that the variables in the analyses were added as interaction terms

Figure 2. The course of anxiety from before treatment to 24-month follow-up, by the associated factor as measured before treatment. All other factors were set at their mean value. A higher score indicated more of anxiety.



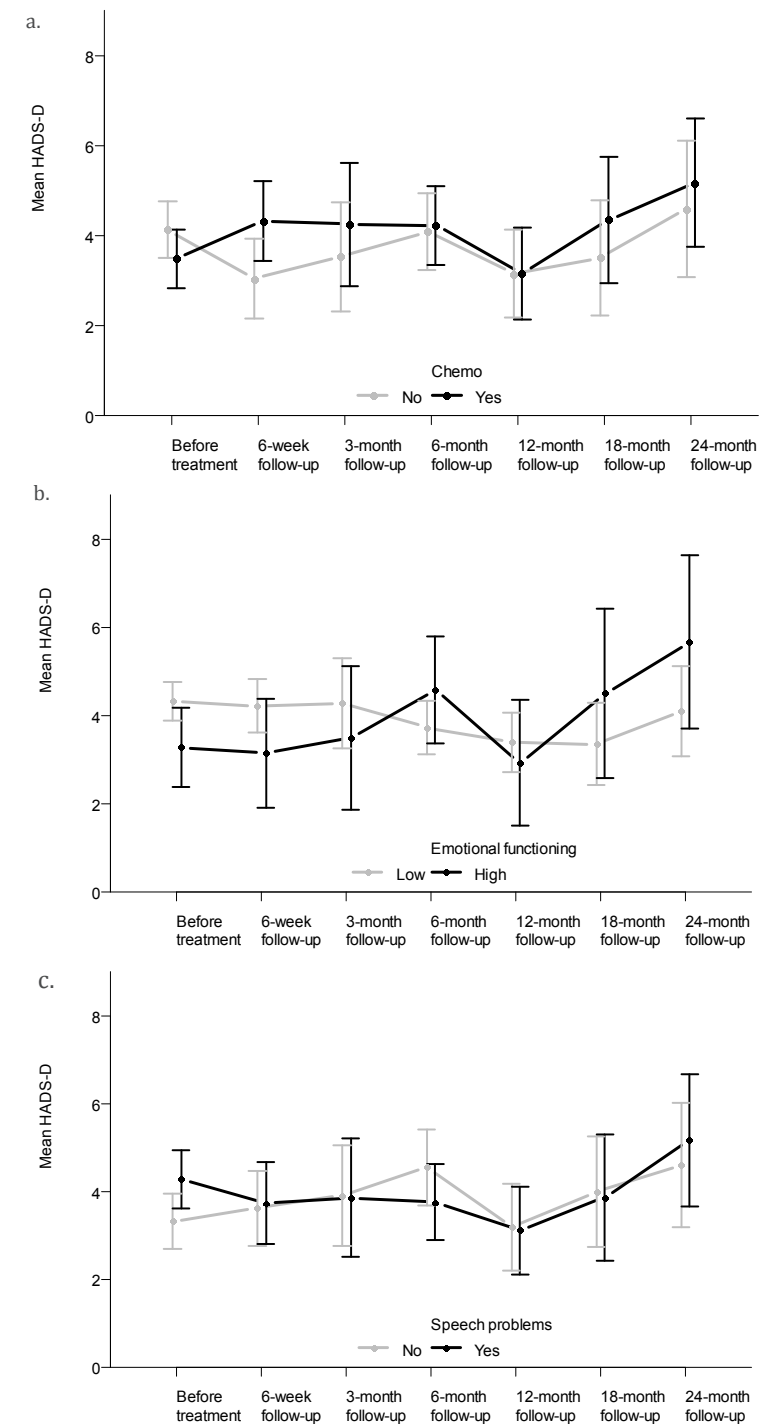
* At baseline, 170 patients were young (<62), 240 patients had pain, 105 patients had trouble with social contact and 49 patients felt ill of all 345 patients. Cut-off points used were pain >9.16, trouble with social contact >1.1 and feeling ill >3.6.

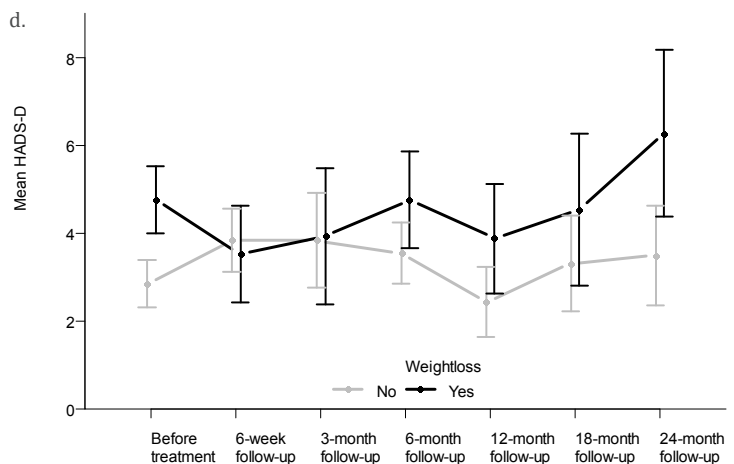
Multivariable analysis showed that chemotherapy ($p=0.019$), and (as measured at 6-month follow-up) cognitive functioning ($p=0.014$), social functioning ($p=0.002$), insomnia ($p=0.029$), swallowing ($p=0.007$) and trouble with social eating ($p<0.001$) were associated with the follow-up course of anxiety (6- to 24-month follow-up) (Table 3 and Appendix B). Patients treated with radiotherapy showed an improvement in anxiety over time, whereas patients treated with chemoradiation did not report a great change in their anxiety over time. Patients with low cognitive functioning reported more anxiety at 6-month follow-up than patients with high cognitive functioning. This difference declined until 12-months follow-up, after which the difference increased again. Patients with low social functioning showed a better course (i.e., scores improved or got worse less at a faster rate over time) of anxiety until 18-month follow-up than patients with high social functioning. However, from 18-month follow-up to 24-month follow-up, patients with a low social functioning showed a poorer course of anxiety. Patients with insomnia showed until 18-month follow-up a better course of anxiety than patients without insomnia. However, from 18-month follow-up to 24-month follow-up, the opposite was seen. Furthermore, patients without swallowing problems showed a substantial improvement in the course of anxiety, whereas patients with swallowing problems did not report a great difference in their anxiety over time. Finally, patients who had trouble with social eating reported more anxiety at 6-month follow-up than patients without trouble with social eating. However, patients with social eating problems showed a better course of anxiety from 6- to 24-month follow-up than the other group.

Factors associated with the course of depression

Multivariate analysis showed that the course of depression from pretreatment to 24-month follow-up was significantly associated with chemotherapy ($p=0.009$), emotional functioning ($p=0.011$), speech problems ($p=0.034$) and weight loss ($p=0.006$) (Table 3 and Figure 3). Patients who received chemotherapy had especially between the first two time points and between 12-month follow-up and 24-month follow up a poorer course of depression than patients who did not receive chemotherapy. Patients with low emotional functioning had a stable course of depression, whereas patients with a high emotional functioning had a poorer course between 12-month follow-up and 24-month follow-up. Patients without speech problems had a poorer course of depression between pretreatment and 6-months follow-up, whereas patients with speech problems had a poorer course between 6-month follow-up and 24-month follow-up. Patients without weight loss had a poorer course of depression between pretreatment and 6-week follow-up than patient with weight loss, whereas from 6-week follow-up to 24-month follow-up, the opposite was seen.

Figure 3. The course of depression from before treatment to 24-month follow-up, by the associated factor as measured before treatment. All other factors were set at their mean value. A higher score indicated more of depression.





*At baseline, 160 patients will receive chemotherapy, 282 patients had a worse emotional functioning, 153 patients had speech problems and 104 patients had weight loss of all 345 patients. Cut-off points used were emotional functioning >90 and speech problems >20.

The multivariate analysis showed that (as measured at 6-month follow-up) nausea and vomiting ($p=0.005$), dyspnea ($p<0.001$), coughing ($p=0.020$) and feeling ill ($p=0.003$) were associated with the follow-up course of depression (from 6- to 24-month follow-up) (Table 3 and Appendix C). Patients with nausea and vomiting showed a poorer course of depression than patients without nausea and vomiting between 6-month follow-up and 12-month follow-up. However, from 12-month follow-up to 24-month follow-up, patients with nausea and vomiting showed an improvement over time, whereas patients without did not report a great difference in their depression. Although patients with dyspnea reported more depression at 6-month follow-up, this group showed a better course of depression until 12-month follow-up than patients without dyspnea. From 12-month follow-up to 24-month follow up, the course of depression improved in both groups. Patient with coughing seem to stay stable over time in their depression, whereas patients without coughing showed an improvement in the course of depression until 18-month follow-up. Finally, although patients who felt ill reported more depression at 6-month follow-up, this group showed an improvement in the course of depression, whereas patients who did not feel ill did not report a great difference in their depression.

Discussion

The aim of this study was to obtain insight in factors associated with the course of anxiety and depression from diagnosis up to two years after treatment. Anxiety was highest at pretreatment (29% of the HNC patients had an increased risk for an anxiety disorder) and gradually decreased to 17% at 6 months after treatment and further decreased to 10% at 24-month follow-up. These findings confirm previous findings among HNC patients^{2,15}. Depression was highest at pretreatment (15% of the HNC patients had an increased risk for a depression disorder) and at 6-weeks (14%) and 3-months (18%) after treatment, which was decreased at 6-months (11%), 12-months (7%), and 18-months (11%) follow-up, and increased again at 24-months follow-up (16%). This pattern up to one year was also observed in the studies of Neilson et al. (2013)⁹ and Astrup et al. (2015) among HNC patients²⁴. The current study showed an increase in depression between 18-month and 24-month follow-up, which has previously not been reported^{3,9,24}. However, at 24-months follow-up there was a good deal of missing data. This was partly due to mortality, but is also possible that especially patients who suffered from depression continued to participate, which might explain the increase in depression²⁵.

Our hypotheses that the course of anxiety would be associated with sociodemographic and clinical factors as well as HRQOL and HNC symptoms, while the course of symptoms of depression would be associated with HRQOL and HNC symptoms rather than sociodemographic and clinical factors, were mostly confirmed. Indeed, the course of anxiety was significantly associated with sociodemographic (younger age) and clinical (receiving chemotherapy compared to radiotherapy only) factors, as well as HRQOL (cognitive and social functioning) and symptoms (pain, insomnia, swallowing, social eating, social contact and feeling ill). In contrast to our hypotheses, chemo(radiation) was associated with the course of depression. On the other hand, as we expected, the course of depression was not associated with sociodemographic factors, but was associated with HRQOL (emotional functioning) and symptoms (nausea, vomiting, dyspnea, speech problems, coughing, feeling ill and weight loss).

From a clinical point of view, it is important to know that younger patients have a higher risk of (developing) anxiety during the first two years after diagnosis. Unfortunately, in this study, the type of anxiety is unknown, but may well be related to fear of recurrence²⁶, which is highly prevalent among HNC patients. Nonetheless, it seems valuable to screen younger patients for anxiety and to offer psychosocial care to those who need it²⁷. The same holds true for patients who receive additional chemotherapy to radiation alone and other groups who are at higher risk for (developing) anxiety and depression during the first 2 years after diagnosis. Psychosocial care targeting HNC patients suffering from anxiety or depression have been shown to be effective and cost-effective^{28,29}.

The fact that symptoms and HRQOL were associated with the course of anxiety and depression, however, raises new research questions. We do not yet understand whether there is a causal relationship or if the found associations were due to clustering of symptoms. A related question refers to the etiology of symptoms. A previous review has shown that several cancer-related symptoms such as pain, fatigue, and depression often coexist in patients³⁰. Two other studies by Chiang et al. (2018)³¹ and Xiou et al. (2013)³² found specific clusters of symptoms among HNC patients, for example a cluster which include dry mouth, lack of appetite, sleep disturbance, fatigue, drowsiness, distress, and sadness. Further research is needed to obtain more insight into these new research questions. Strengths of this study were the wide range of HRQOL factors and symptoms that were investigated in relation to the course of anxiety and depression, the longitudinal design with six follow-up time points and the relatively large sample size. In addition, a homogeneous study sample of HNC patients treated with primary (chemo)radiation with curative intent was included. Although this is a strength, it may limit representativeness to the entire population of HNC patients.

Furthermore, it is unknown whether patients received psychosocial care during this study and therefore we were unable to control for these possible effects. Additionally, not all patients were involved in every follow-up measure, partly due to the observational study design. Sample sizes were particularly small at 3-, 18- and 24-month follow-up. However, the mixed model analyses enabled the inclusion of patients who did not complete every measure. We are also limited due to our use of self-reported measures of anxiety and depression as compared to a Structured Clinical Interview for DSM-IV³³. Another limitation was not being aware of the HPV status of patients. This is potentially important in oral/ oropharyngeal patients. Finally, it is not clear yet whether the actual association between the symptoms and HRQOL and anxiety and depression is based on a causal relation or that there is an underlying factor which may explain clustering (e.g., disrupted immune system).

From a clinical point of view these findings support the need of tailored care, that not only take the level of anxiety and depression into account, but also symptom burden which may coexist. More longitudinal research on factors that are associated with the course of anxiety and depression in HNC patients is necessary to be able to substantiate current investigated factors and to identify other associated factors. Previous research suggest, for example, that personal protective factors (e.g., resilience, physical health, meaning, social support, autonomy, coping style) may also be associated with anxiety and depression^{10,13}. Furthermore, biomarkers related to hypothalamic-pituitary-adrenal (HPA)-axis functioning and a history of depression may be related to a depression³⁴⁻³⁶. However, biological factors in relation to depression may also help us understand possible underlying biological mechanisms of clustering of HNC-specific

clusters. An ongoing longitudinal cohort study called the NETHERlands Quality of life and Biomedical Cohort studies in Head and Neck Cancer (NET-QUBIC) is investigating this now, enabling us to investigate socio-demographic, clinical and personal factors, biomarkers, and history of depression and anxiety in relation to the course of symptoms of depression as well as the development of clinical depression over time³⁷.

Conclusion

In conclusion, symptoms of anxiety and depression are common in HNC patients in the first two years after diagnosis. Associated factors are younger age (anxiety), treatment with chemotherapy and worse HRQOL and higher symptom burden (both anxiety and depression).

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Appendix

Appendix A, Appendix B and Appendix C are available online at <https://www.sciencedirect.com/science/article/pii/S1368837520300129>.

Chapter 4

Psychological problems among head and neck
cancer patients in relation to utilization of
healthcare and informal care and costs in the first
two years after diagnosis

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Summary

Purpose

To investigate associations between psychological problems and the use of healthcare and informal care and total costs among head and neck cancer (HNC) patients.

Method

Data were used of the NETHERlands QUALity of Life and Biomedical Cohort study. Anxiety and depression disorder (diagnostic interview), distress, symptoms of anxiety and depression (HADS), and fear of cancer recurrence (FCR) and cancer worry scale (CWS) were measured at baseline and at 12-month follow-up. Care use and costs (questionnaire) were measured at baseline, 3-, 6-, 12-, and 24-month follow-up. Associations between psychological problems and care use/costs were investigated using logistic and multiple regression analyses.

Results

Data of 558 patients were used. Distress, symptoms of anxiety or depression, FCR, and/or anxiety disorder at baseline were significantly associated with higher use of primary care, supportive care, and/or informal care (odds ratios (ORs) between 1.55 and 4.76). Symptoms of anxiety, FCR, and/or depression disorder at 12-month follow-up were significantly associated with use of primary care, supportive care, and/or informal care (ORs between 1.74 and 6.42). Distress, symptoms of anxiety, and FCR at baseline were associated with higher total costs.

Conclusions

HNC patients with psychological problems make more use of healthcare and informal care and have higher costs. This is not the result of worse clinical outcomes.

Introduction

Head and neck cancer (HNC) patients are prone to psychological problems. In this exploratory study, psychological problems are defined as symptoms of depression, symptoms of anxiety, distress, fear of cancer recurrence (FCR), depression disorder, or anxiety disorder. Prevalence rates of distress range from 29% to 53%^{1,2,3}. It is estimated that symptoms of anxiety are present in approximately 10% to 29%^{4,5}, and symptoms of depression in 15% to 50%, of HNC patients^{5,6,7,8,9,10}. Prevalence rate of high FCR is estimated at 53% among HNC patients¹¹. These psychological problems, besides influencing a patients' health-related quality of life¹², may also have economic consequences due to higher healthcare use¹³.

Carlson and Bultz¹³ previously suggested that cancer patients with psychological problems not only have increased mental healthcare use, but may also make more use of other healthcare domains, such as inpatient healthcare and general practitioner visits. A recent systematic review investigating psychological problems in relation to healthcare and societal costs among cancer patients in general, supported this suggestion¹⁴. This review showed that there is strong evidence for a significant association between anxiety and depression disorders and increased inpatient and outpatient healthcare use. When focusing on psychological symptoms (rather than disorders), FCR was found to be significantly associated with increased primary care use¹⁵. For other associations between psychological symptoms (FCR, distress, symptoms of depression, and symptoms of anxiety) and healthcare use (inpatient, primary, mental, and supportive care) the results were inconclusive due to inconsistent findings or limited evidence available¹⁴. No studies were conducted that investigated the association between psychological problems and informal care use. This review also showed that most previous research was conducted among breast cancer patients and cancer patients in general, and only a few studies targeted other specific tumor sites, such as HNC. Existing evidence on the associations between psychological problems and healthcare use may not be representative of HNC patients, as differences in sociodemographic and clinical characteristics, and differences in the prevalence of psychological problems, may influence this association. Furthermore, as studies have shown that HNC patients report one of the highest prevalences of any mental disorder in a life time and currently among all cancer types^{10,16}, investigating the relationship between healthcare use and costs among this cancer patient subgroup is especially important. So far, only two studies have investigated the association between psychological problems and medical healthcare use among HNC patients^{17,18}. A cross-sectional study by Laurence et al.¹⁸ found that, among 34,153 HNC patients, depression disorder was associated with more hospital admissions. Another cross-sectional study by Jeffery et al. found that, among 2944 HNC patients, depression and

anxiety disorders were associated with more hospital admissions, ambulatory visits, and the number of bed days in hospital¹⁷. However, there are no longitudinal studies to date that investigate the association between psychological problems and mental healthcare, primary care, supportive care, and/or informal care among HNC patients.

This exploratory study aimed to investigate the relationship between psychological problems in relation to healthcare utilization (mental healthcare, primary care, and supportive care), use of informal care, and the costs, from baseline (before the start of treatment) up to 2 years after treatment, among HNC patients.

Methods

Patients and procedure

Data from the NETHERlands QUality of Life and Biomedical Cohort (NET-QUBIC), an ongoing prospective observational cohort study among newly diagnosed HNC patients in the Netherlands, were used¹⁹. Patients were recruited between March 2014 and June 2018. Patients were included in NET-QUBIC if they were (1) 18 years or older; (2) treated with curative intent for cancer of the oral cavity, oropharynx, hypopharynx, larynx, or unknown primary; (3) able to write, read, and speak Dutch; and (4) if they completed the medical consumption questionnaire (iMCQ) at baseline. Exclusion criteria were severe psychiatric comorbidities (schizophrenia, Korsakoff's syndrome, severe dementia). Consent procedures were approved by the Medical Ethical Committee of VUmc and followed the Dutch Medical Research Involving Human Subjects Act (METc VUmc 2013.301). The NET-QUBIC Data Warehouse comprises data derived from an electronic clinical report form (eCRF) (assessed at baseline, 24-, and 60-month follow-up); patient-reported outcome measures (PROMs); at baseline (shortly after diagnosis and before start of treatment); at 3-, 6-, 12-, 24-, 36-, 48-, and 60-month follow-up (after finishing cancer treatment); and fieldwork assessments (at baseline, 6-, 12-, 24-, and 60-month follow-up). In this study, baseline eCRF data were used, as well as PROM data collected at baseline and at 3-, 6-, 12-, and 24-month follow-up. From the fieldwork assessments, we used data from the psychiatric interview (Composite International Diagnostic Interview (CIDI)) collected at baseline and at 12-month follow-up.

Outcome measures

Demographic and clinical characteristics were collected by PROMs and eCRF data. Demographic factors included sex, age, education (low/middle/high), and living status (alone/cohabiting). Clinical factors included tumor location (oral cavity/oropharynx, hypopharynx, larynx), tumor stage (0–II/III–IV), treatment modality (single/multimodality treatment), World Health Organization performance status (0, able to

carry out all normal activity without restriction; ≥ 1 , restricted in normal activities). Comorbidity was assessed by the 27-item Adult Comorbidity Evaluation-27 Index, which categorizes comorbidity as none–mild, and moderate–severe²⁰.

Symptoms of anxiety, depression, and distress were measured with the Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item questionnaire measuring symptoms of anxiety (subscale HADS-A) and depression (subscale HADS-D)²¹. Patients respond to all items on a 4-point Likert scale, resulting in a subscale score ranging from 0 to 21. A higher score indicates higher extent of depression or anxiety symptoms. A subscale score of ≥ 8 was used to identify patients with symptoms of anxiety or depression. A total score of ≥ 11 was used to identify patients with distress. Internal consistency in this study was good (Cronbach's alpha ranged from 0.78 to 0.89).

Fear of cancer recurrence was measured with the Cancer Worry Scale (CWS)²². The CWS is an 8-item questionnaire measuring concerns about developing cancer or developing cancer again, and the effect of these concerns on daily life. Patients respond to all items on a 4-point Likert scale, resulting in a subscale score ranging from 8 to 32. A higher score indicates higher extent of FCR. A cut-off at ≥ 14 for the total score was used to identify patients with a high level of FCR²². The Dutch version of CWS is validated in various cancer populations^{23,24}. Internal consistency was good in this HNC study population (Cronbach's alpha was 0.89). Anxiety disorder and depression disorder in the past 6 (baseline) or 12 (12-month follow-up) months was assessed with the Composite International Diagnostic Interview (CIDI), which is based on DSM-IV criteria²⁵. Fieldworkers from different backgrounds (e.g., nurse, dietician, psychologist) were trained to conduct the CIDI in a standardized way. All CIDI interviews were audiotaped and randomly checked for their quality. Healthcare use was measured with the iMCQ developed by the Institute for Medical Technology Assessment (iMTA) of the Erasmus University Rotterdam, the Netherlands^{26,27}. This questionnaire measures healthcare use with a recall period of 3 months. In this study, we specifically investigated the use of (1) mental healthcare (psychiatrist, psychologist, or psychotherapist visits); (2) primary care (general practitioner visits and phone calls); (3) supportive care (physiotherapy, speech therapy, oral hygiene care, dietetics, social work, support groups); and (4) informal care (support from family, friends, neighbors, colleagues). In cases where data on the number of visits were missing (e.g., a patient reported to have visited a general practitioner, but did not report the number of visits), assumptions were made based on the means of participants who used this type of care, per measurement.

Total costs (mental healthcare, primary care, supportive care, and informal care costs) were calculated by multiplying resource use by the integral cost price from a Dutch cost price manual²⁸. All prices were converted to 2018 prices using the consumer price index.

Statistical analysis

Baseline characteristics of the study population are described using their mean and standard deviation, and percentage. Differences between included and excluded patients were investigated using independent t-tests for continuous variables and chi-square tests for categorical variables. A p-value lower than 0.05 was considered statistically significant. Associations between psychological problems and healthcare use (yes/no) were analyzed using chi-square tests (univariate analyses) and logistic regression analyses (multivariate analyses). Scores on symptoms of anxiety and depression, distress, and fear of recurrence were dichotomized based on validated cut-off scores, as described above. The potential confounding role of age, sex, living status, education level, tumor site, tumor stage, treatment, performance status, and comorbidity were investigated using forward logistic regression analyses. Only potential confounding factors that were significantly associated with healthcare use (p-value for entry of <0.05) were included in the final multivariate model. Odds ratios (OR) were calculated as a measure of effect size, and represent the increased odds for care use in HNC patients with psychological problems compared to those without.

The association between psychological problems and healthcare costs was analyzed using multiple regression analyses corrected for all above-mentioned variables. Since cost data are usually characterized by a non-normal distribution and high variance, studies are seldom powered to detect significant differences in costs among groups²⁹. Therefore, a probabilistic approach was used. Bias-corrected and accelerated bootstrap confidence intervals (BCa CI) were generated by replicating the regression analyses using bias-corrected and accelerated bootstrapping with 5000 replications.

Analyses were carried out investigating psychological problems before treatment in relation to care use and costs at baseline, as well as at 3-, 6-, 12-, and 24-month follow-up. Furthermore, analyses were carried out investigating psychological problems at 12 months after treatment in relation to care use and costs at 12- and 24-month follow-up. All statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) and R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Of the 739 eligible patients, 181 patients (25%) did not fill in the iMCQ at baseline, resulting in a study population of 558 patients. Patients who were included in this specific study often lived with others, were more often diagnosed with tumor stage I

or II, and often had a better WHO performance state and less comorbidity, compared to those who were not included (p < 0.05).

The characteristics of the study population are shown in Table 1. The majority were male (74%) and the mean age was 64 years (range 19–86 years). Most patients had a stage III–IV tumor (57%). The tumors were most often located in the oropharynx (36%), followed by an oral cavity (28%), larynx (27%), hypopharynx (6%), and unknown primary (3%). Approximately one third of the patients (33%) were treated with radiotherapy, 21% of the patients were treated with surgery, and 45% of the patients were treated with a combination of treatment modalities (chemoradiation, or surgery and (chemo)radiotherapy). In total, 88% of all 558 patients included in this study completed at least one follow-up measure (Figure 1). Reasons for drop-out are shown in Figure 1. More detailed information on the study flow is provided in a previous published study³⁰.

Table 1. Characteristics of included and excluded patients.

	Excluded Patients (n = 181)	Included Patients ² (n = 558)	p-value
Mean age (SD)	62 (11)	64 (9)	0.07
Women	43 (24%)	147 (26%)	0.49
Living alone	57 (43%)	106 (21%)	<0.01
Education level ¹			
Low	64 (48%)	215 (42%)	0.13
Middle	37 (28%)	134 (26%)	
High	31 (24%)	167 (32%)	
Tumor site			
Oral cavity	43 (24%)	156 (28%)	0.36
Oropharynx	63 (35%)	199 (36%)	
HPV positive	26 (41%)	104 (52%)	
HPV negative	30 (48%)	69 (35%)	
HPV unknown	7 (11%)	26 (13%)	
Hypopharynx	18 (10%)	34 (6%)	
Larynx	53 (29%)	152 (27%)	
Unknown primary	4 (2%)	17 (3%)	
Clinical tumor stage ³			
0/I/II	57 (31%)	238 (43%)	0.01
III/IV	124 (69%)	320 (57%)	
Treatment			
Surgery	36 (20%)	116 (21%)	0.37
Radiotherapy	56 (31%)	185 (33%)	
Chemoradiotherapy	62 (34%)	153 (27%)	
Surgery and radiotherapy	20 (11%)	86 (15%)	
Surgery and chemoradiotherapy	6 (3%)	17 (3%)	
WHO performance status			
0	112 (62%)	395 (71%)	0.03
1 or more	69 (38%)	163 (29%)	
ACE-27 comorbidity			
None/mild	97 (58%)	371 (70%)	<0.01
Moderate/severe	71 (42%)	160 (30%)	

Table 1. Continued

	Excluded Patients (n = 181)	Included Patients ² (n = 558)	p-value
Psychological outcomes at baseline			
High level of distress (HADS-T ≥ 11)		206 (37%)	
Symptoms of anxiety (HADS-A ≥ 8)		146 (26%)	
Symptoms of depression (HADS-D ≥ 8)		80 (14%)	
High level of fear of recurrence (CWS ≥ 14)		251 (46%)	
Anxiety disorder		11 (2%)	
Depression disorder		14 (3%)	

(1) Low education level includes primary education, lower or preparatory vocational education, and intermediary general secondary education. Middle education level includes senior general secondary education and higher general secondary education. High education level includes higher professional education and university. (2) There were 41 missing values on living status, 42 missing values on education level, 1 missing value on treatment, 27 missing values on comorbidity, 4 missing values on increased distress, 4 missing values on increased anxiety, 2 missing values on increased depression, 14 missing values on fear of cancer recurrence, 108 missing values on anxiety disorder, 109 missing values on depression disorder. (3) One patient had a clinical TNM of 0 and a pathological TNM of II, and was therefore included in the NET-QUBIC study. Abbreviations: HADS, Hospital Anxiety and Depression Scale; T, total; D, depression; A, anxiety; HPV, human

The prevalence rate of a high level of distress was 33% at baseline, and 17% at 12-month follow-up. The prevalence rate of symptoms of anxiety was 26% at baseline and 9% at 12-month follow-up, and of symptoms of depression was 14% at baseline and 9% at 12-month follow-up. FCR was found in 37% of the patients at baseline and 29% at 12-month follow-up. The prevalence rates of anxiety and depression disorders were substantially lower; 2% and 3% at baseline and 1% and 6% at 12-month follow-up, respectively.

Use of healthcare and informal care

Frequencies of healthcare and informal care use are presented in Table 2. Use of mental healthcare was relatively low at all time points (<9%). Use of primary care ranged from 92% at baseline to 57–59% at 12- and 24-month follow-up. Use of supportive care ranged from 54–80%, of which physical therapy, dietician care, and oral hygiene care were used most often, and social work and support groups were used less often (<5%). The use of informal care ranged from 9–24%.

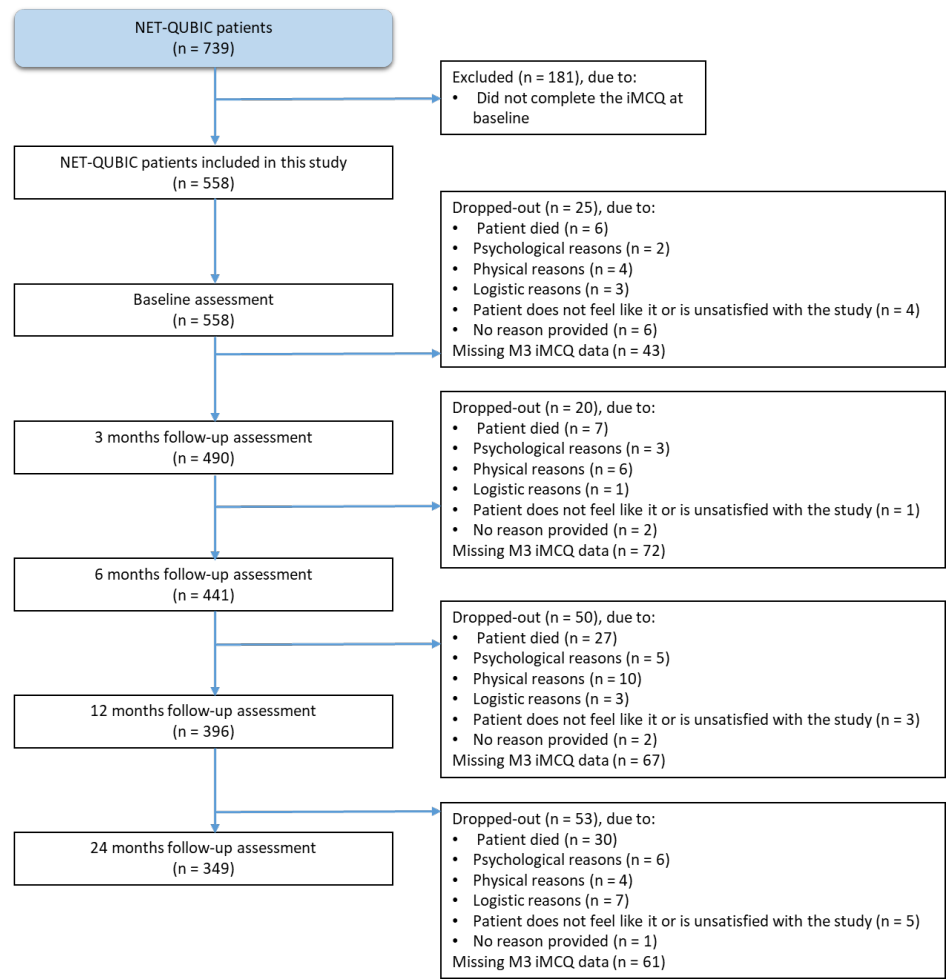
Patients who used mental healthcare and primary care reported, on average, three to four visits in the previous 3 months. Patients who used supportive care reported, on average, four to nine visits, and patients who used informal care received, on average, between 29 and 58 h of care in the last 3 months.

Psychological problems in relation to use of healthcare and informal care

Results of univariate analyses testing psychological problems in relation to healthcare and informal care use are shown in Appendix A and Appendix B. Psychological problems that were significantly associated with care use in the univariate models were further

analyzed in multivariate analyses with correction for potential confounders (Table 3); this excludes the associations with mental healthcare use, as a consequence of low mental healthcare use. Distress, symptoms of anxiety, symptoms of depression, FCR, anxiety disorder, and depression disorder were significantly associated with higher mental healthcare use for at least one time point. Use of mental healthcare ranged from 3% to 7% among patients without psychological problems, and from 6% to 50% among patients with psychological problems (Appendix A and Appendix B). Anxiety disorder at 12-month follow-up in relation to care use could not be analyzed due to an insufficient sample size (i.e., <10 patients with an anxiety disorder at 12-month follow-up).

Figure 1. Flow diagram.



*Medical consumption questionnaire (iMCQ).

Table 2. Use of care at baseline, 3-, 6-, 12-, and 24-month follow-up.

	Baseline (N = 558)			3-Month Follow-Up (N = 490)			6-Month Follow-Up (N = 441)			12-Month Follow-Up (N = 396)			24-Month Follow-Up (N = 349)		
	% patients using service	Mean number (SD) of contacts or hours *	% patients using service	% patients using service	Mean number (SD) of contacts or hours *	% patients using service	% patients using service	Mean number (SD) of contacts or hours *	% patients using service	Mean number (SD) of contacts or hours *	% patients using service	Mean number (SD) of contacts or hours *	% patients using service	Mean number (SD) of contacts or hours *	% patients using service
Mental healthcare	3%	4.4 (6.4)	8%	8%	2.9 (2.7)	8%	8%	4.1 (3.5)	8%	3.0 (2.8)	4%	4.1 (3.8)	4%	4.1 (3.8)	4%
Primary care	92%	3.8 (3.3)	76%	76%	4.2 (4.3)	66%	66%	3.6 (4.5)	57%	3.3 (2.6)	59%	4.5 (20.7)	59%	4.5 (20.7)	59%
Supportive care	58%	4.3 (6.2)	80%	80%	7.8 (9.2)	71%	71%	9.0 (12.4)	60%	7.7 (11.5)	54%	7.06 (12.2)	54%	7.06 (12.2)	54%
Social work	4%	3.5 (4.7)	4%	4%	6.8 (5.7)	5%	5%	1.7 (1.6)	4%	3.4 (4.7)	4%	10.1 (12.1)	4%	10.1 (12.1)	4%
Physical therapy	13%	8.3 (8.0)	22%	22%	8.1 (6.3)	32%	32%	11.7 (10.9)	26%	10.4 (10.4)	25%	6.2 (13.0)	25%	6.2 (13.0)	25%
Support group	1%	12.3 (8.2)	4%	4%	6.9 (5.8)	5%	5%	19.4 (15.8)	4%	14.8 (11.4)	2%	10.75 (10.7)	2%	10.75 (10.7)	2%
Dietitian	27%	1.4 (1.3)	56%	56%	3.0 (3.5)	27%	27%	1.9 (1.6)	12%	2.0 (1.7)	8%	1.6 (0.9)	8%	1.6 (0.9)	8%
Speech therapy	9%	2.1 (2.1)	18%	18%	2.8 (5.6)	16%	16%	3.3 (3.8)	11%	4.9 (6.1)	6%	5.7 (6.7)	6%	5.7 (6.7)	6%
Oral care	38%	1.3 (0.7)	52%	52%	3.5 (6.1)	39%	39%	1.5 (1.2)	34%	1.3 (0.9)	28%	1.2 (1.0)	28%	1.2 (1.0)	28%
Informal care	13%	29.3 (39.4)	24%	24%	61.0 (97.2)	17%	17%	46.9 (90.4)	13%	49.2 (63.9)	9%	57.6 (74.7)	9%	57.6 (74.7)	9%

* Informal care and support group were measured in hours. Healthcare use and informal care were measured with a recall period of 3 months.

Table 3. Multivariate analyses testing associations between psychological problems at baseline and 12- months follow-up and use of care at baseline, 3-,6-,12-, and 24-month follow-up.

	Baseline (N = 558)		3-Month Follow-Up (N = 490)		6-Month Follow-Up (N = 441)		12-Month Follow-Up (N = 396)		24-Month Follow-Up (N = 396)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Measured at baseline										
Distress										
Mental healthcare										
Primary care			N/A		N/A		N/A		N/A	
Supportive care	1.59 (1.09-2.32)	0.02					1.74 (1.13-2.67)	0.01	1.78 (1.11-2.87)	0.02
Informal care	1.48 (0.86-2.53)	0.16	1.36 (0.85-2.18)	0.20						
Mental healthcare			N/A		N/A					
Primary care	2.54 (1.05-6.11)	0.04			1.61 (0.99-2.62)	0.057	1.77 (1.10-2.87)	0.02	1.99 (1.17-3.36)	0.01
Supportive care	1.55 (1.02-2.36)	0.04	1.98 (1.07-3.67)	0.03						
Informal care			1.57 (0.94-2.60)	0.08	1.27 (0.70-2.31)	0.440				
Mental healthcare					N/A				1.54 (0.75-3.16)	0.24
Primary care										
Supportive care										
Informal care										
Mental healthcare	1.68 (0.87-3.23)	0.12	1.62 (0.89-2.95)	0.12	2.58 (1.34-4.97)	0.005				
Primary care			N/A		N/A					
Supportive care										
Informal care										
Mental healthcare			1.64 (1.00-2.70)	0.05			1.60 (1.06-2.40)	0.03	1.47 (0.94-2.29)	0.09
Primary care			1.71 (1.06-2.76)	0.03						
Supportive care										
Informal care										
Mental healthcare										
Primary care										
Supportive care										
Informal care										
Mental healthcare			4.76 (1.04-21.81)	0.045						
Primary care	N/A		N/A		N/A					
Supportive care										
Informal care										
Mental healthcare										
Primary care										
Supportive care										
Informal care										

Table 3. Continued

Measured at 12-months follow-up		Baseline (N = 558)		3-Month Follow-Up (N = 490)		6-Month Follow-Up (N = 441)		12-Month Follow-Up (N = 396)		24-Month Follow-Up (N = 396)	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Distress	Mental healthcare	N/A									
	Primary care										
	Supportive care										
Symptoms of anxiety	Informal care										
	Mental healthcare										
	Primary care										
Symptoms of depression	Supportive care										
	Informal care										
	Mental healthcare										
Fear of cancer recurrence	Primary care										
	Supportive care										
	Informal care										
Depression disorder	Mental healthcare										
	Primary care										
	Supportive care										
	Informal care										
		6.42 (1.64-9.81)									
		0.01									

Abbreviations: N/A, not applicable due to insufficient sample size; CI, confidence interval; OR, odds ratio. Odds ratios are adjusted for age, sex, living status, education level, tumor site, tumor stage, treatment, performance state, comorbidity. Bold represents significance ($p < 0.05$).

With regard to associations between psychological problems and primary, supportive, and informal care use, multivariate analyses showed that symptoms of distress at baseline were significantly associated with use of primary care at 12-month follow-up (OR = 1.74, 95% CI = 1.13–2.67) and use of supportive care at baseline (OR = 1.59, 95% CI = 1.09–2.32) and 24-month follow-up (OR = 1.78, 95% CI = 1.11–2.87). Symptoms of anxiety were significantly associated with use of primary care at baseline (OR = 2.54, 95% CI = 1.05–6.11) and 12-month follow-up (OR = 1.77, 95% CI = 1.10–2.87), and use of supportive care at baseline (OR = 1.55, 95% CI = 1.02–2.36), 3-month follow-up (OR = 1.98, 95% CI = 1.07–3.67), and 24-month follow-up (OR = 1.99, 95% CI = 1.17–3.61). Symptoms of depression were significantly associated with use of informal care at 6-month follow-up (OR = 2.58, 95% CI = 1.34–4.97). Symptoms of FCR were significantly associated with use of primary care at 12-month follow-up (OR = 1.60, 95% CI = 1.06–2.40) and use of informal care at 3-month follow-up (OR = 1.71, 95% CI = 1.06–2.76). Anxiety disorder was significantly associated with use of informal care at 3-month follow-up (OR = 4.76, 95% CI = 1.04–21.81).

With regard to psychological problems as measured at 12-months follow-up, multivariate analysis showed that symptoms of anxiety were significantly associated with use of primary care at 12-month follow-up (OR = 2.71, 95% CI = 1.11–6.62). FCR was associated with use of supportive care at 24-month follow-up (OR = 1.74, 95% CI = 1.01–2.98). Depression disorder was associated with informal care use at 24-month follow-up (OR = 6.42, 95% CI = 1.64–9.81).

Psychological problems in relation to costs

Results of the analyses regarding associations between psychological problems at baseline, and costs at baseline, 3-, 6-, 12-, and 24-month follow-up, adjusted for sociodemographic and clinical factors, are shown in Table 4. Psychological distress, symptoms of anxiety, and FCR at baseline were significantly associated with higher costs in the 3 months before baseline assessment (probability >98.3%). Patients with distress at baseline had, on average, €93 (BCa 95% CI = €18; €180) higher costs at baseline, patients with symptoms of anxiety at baseline had, on average, €125 (BCa 95% CI = €45; €231) higher costs at baseline, and patients with FCR at baseline had, on average, €80 (BCa 95% CI = €10; €162) higher costs at baseline, compared to patients without these psychological problems.

Results of the analyses for the associations between psychological problems at 12-month follow-up, and costs at 12- and 24-month follow-up, adjusted for sociodemographic and clinical factors, are shown in Table 4. None of the associations were statistically significant. However, the probability approach showed that the probability that anxiety disorder at baseline was associated with higher costs at 6-month follow-up was

Table 4. Differences in costs at baseline, 3-, 6-, 12-, and 24-month follow-up between patients with and without psychological problems at baseline and 12-months follow-up

	Baseline		3-Month Follow-Up		6-Month Follow-Up		12-Month Follow-Up		24-Month Follow-Up	
	Mean (95% BCa CI)	% *	Mean (95% BCa CI)	% *	Mean (95% BCa CI)	% *	Mean (95% BCa CI)	% *	Mean (95% BCa CI)	% *
Measured at baseline										
Distress	€93 (18; 180)	99.1%	€21 (-230; 214)	58.7%	€-58 (-283; 90)	28.2%	€-5 (-158; 141)	48.7%	€100 (-105; 534)	74.1%
Symptoms of anxiety	€125 (45; 231)	99.7%	€-40 (-252; 203)	34.5%	€-83 (-291; 81)	19.1%	€-15 (-166; 149)	42.6%	€-12 (-248; 182)	45.3%
Symptoms of depression	€49 (-79; 215)	76.1%	€24 (-203; 311)	56.3%	€-85 (268; 145)	20.3%	€-30 (-194; 196)	36.1%	€-104 (-328; 168)	19.9%
Fear of cancer recurrence	€80 (10; 162)	98.3%	€-66 (-273; 98)	24.5%	€-18 (-194; 127)	42.6%	€94 (-58; 276)	87.8%	€4 (-185; 141)	52.4%
Anxiety disorder	€-68 (-277; 141)	26.1%	€393 (-301; 2706)	69.1%	€418 (-128; 1391)	89.3%	€262 (-149; 1086)	82.1%	€-167 (-847; 177)	23.6%
Depression disorder	€89 (-156; 646)	68.2%	€547 (-41; 2077)	91.1%	€388 (-108; 1238)	89.9%	€422 (-21; 1045)	95.1%	€-284 (-705; 36)	5.2%
Measured at 12-months follow-up										
Distress							€166 (-58; 477)	89.6%	€-33 (-247; 215)	37.0%
Symptoms of anxiety							€42 (-161; 406)	60.8%	€124 (-167; 570)	75.1%
Symptoms of depression							€165 (-85; 660)	82.7%	€20 (-196; 574)	51.0%
Fear of cancer recurrence							€89 (-120; 498)	72.0%	€67 (-118; 236)	76.3%
Depression disorder							€-81 (-286; 258)	26.1%	€391 (-188; 1061)	89.6%

Abbreviations: BCa CI, bias-corrected and accelerated bootstrap confidence intervals. * Probability that the group with psychological problems had higher costs. Results are adjusted for age, sex, living status, education level, tumor site, treatment, performance state, comorbidity. Bold represents significance ($p < 0.05$).

high (probability of 89.3%). Furthermore, the probability that depression disorder at baseline was associated with higher costs at 3-, 6-, and 12-month follow-up, and that depression disorder at 12-month follow-up was associated with higher costs at 24-month follow-up, was high (probability between 89.6% and 95.1%). On the other hand, the probability that depression disorder at baseline was associated with higher costs at 24-month follow-up was low (probability of 5.2%).

Discussion

The aim of this study was to investigate the relationship between psychological problems and use of care and costs from baseline up to 2 years after treatment among HNC patients. Overall, the results of this study support the suggestion posed by Carlson and Bultz¹³ that cancer patients with psychological problems not only make more use of mental healthcare, but also other types of healthcare. The results are also in line with the general findings of a systematic review that cancer patients with psychological problems make more use of mental and primary healthcare, and have higher healthcare costs¹⁴.

In this exploratory prospective study, we specifically investigated the relationship between various types of psychological problems (distress, symptoms of anxiety and depression, FCR, and anxiety and depression disorder) and various types of care (mental, primary, supportive, and informal care) and costs. We found that HNC patients with distress, symptoms of anxiety, or FCR at time of diagnosis had significantly more costs in the 3 months prior to diagnosis. It was also highly likely that patients with psychological problems at baseline had more costs compared to patients without psychological problems at 3- (depression disorder), 6- (anxiety and depression disorder), and 12- (depression disorder) month follow-up, and that patients with psychological problems 12 months after treatment had higher costs at 12- (distress) and 24- (depression disorder) month follow-up. In addition, patients with symptoms of anxiety at baseline made more use of primary care and supportive care, and patients with FCR or an anxiety disorder used informal care more often, 3 months after treatment. Patients with symptoms of depression at baseline made more use of informal care 6 months after treatment, and patients who had distress, symptoms of anxiety, or FCR more often made use of primary care at 12-month follow-up. Patients with symptoms of anxiety at 12-month follow-up made more use of primary care at that assessment time. Two years after treatment, patients with psychological problems at baseline or 12-month follow-up did not seem to make use of primary care as often, but made more use of supportive care (patients with distress or symptoms of anxiety at baseline, and patients with FCR at 12-month follow-up) and informal care (patients

with a depression disorder at 12-month follow-up).

The costs among patients with psychological problems before treatment and/or 12 months after treatment were, when likely to be more expensive (i.e., probability >89%), on average between €80 and €391 higher during a 3-month time period compared to patients without these psychological problems. Other studies reported that cancer patients with a depression disorder or anxiety disorder had, on average, between \$6000 to \$25,000 and \$15,000 to \$60,000 higher costs, respectively, in a year^{17,31,32,33}. A reason for this cost difference might be that, in our study, only costs related to mental, primary, supportive and informal care were included, whereas in these other studies, additional costs of inpatient, outpatient, and emergency room visits were included. Another explanation may be that these other studies focused on psychiatric disorders, and increased care use and costs are especially prevalent among those with psychiatric disorders.

An explanation for the higher costs among patients with psychological symptoms or disorders may be that patients with a poorer clinical status (comorbidity, more advanced cancer stage) are more likely to develop psychological symptoms or a psychiatric disorder^{7,34}. Therefore, higher healthcare use among those with psychological symptoms/disorders might not be a result of psychological symptoms/disorder, but instead be a result of a poorer clinical status. To account for this, we adjusted for confounders at baseline, such as cancer stage, treatment modalities, and comorbidity. Although some associations were no longer significant after adjustment, several associations remained significant, indicating that associations between psychological problems and healthcare use and costs do not (entirely) result from worse clinical outcomes.

Other explanations for higher care use and costs among those with psychological symptoms or disorders, as previously hypothesized by Carlson and Bultz¹³, are that patients with psychological problems may be less likely to fully adhere to medical treatment, and that they are less likely to maintain a healthy lifestyle; these factors may lead to decreased overall health at follow-up, and, consequently, an increased need for and use of healthcare services. Surprisingly, results at 24-month follow-up suggest that patients with psychological problems at baseline have lower costs. An explanation for this may be that the association between psychological problems and costs is especially present at short-term follow-up, and that later on, other factors become more important in the association with costs. In the current study, it seems that patients with a psychiatric disorder made solely more use of informal care (and not professional primary or supportive care), whereas patients with distress, symptoms of anxiety or depression, or FCR made more use of professional care (i.e., primary care and supportive care). Due to limited power, the use of mental healthcare could

not be investigated via multivariate models. However, univariate analyses showed that mental healthcare was used relatively more often by patients with a psychiatric disorder (mental health care was used by up to 40% of patients with a disorder at baseline versus 16% among patients with psychological symptoms). This suggests that patients with a psychiatric disorder are more likely to be referred to mental healthcare, whereas patients with psychological symptoms may be more likely to be referred to supportive care, or to consult their general practitioner. Another observation is that, seemingly, patients with symptoms of depression, or a depression disorder, made more use of informal care, whereas patients with symptoms of anxiety, FCR, or an anxiety disorder, made more use of both primary care and informal care. An explanation for this may be that anxious patients visit healthcare providers more often to be reassured that their health is under control.

To unravel these potential differences, further research is needed on the course of healthcare utilization after diagnosis, and the moderation or mediating effects of psychological problems, cancer recurrence, lifestyle behavior, and treatment adherence. The use of mental healthcare in this study population was low, which may be related to suboptimal organization of care and/or willingness to accept mental healthcare by patients. Brebach et al.³⁵ estimated that 60% of cancer patients with distress, anxiety, or depression accept psychological treatment when offered³⁵. This percentage was also reported in a recent study among mixed cancer patients with adjustment disorders³⁶. Further research is needed on factors that may explain why some patients receive psychological care in clinical practice and some do not, including the role of the patient him/herself (e.g., coping style, a self-perceived need for psychological care).

A key strength of this study is the longitudinal design, which enabled prospective analyses of associations between psychological problems and care use and costs. Another strength of this study is that patient-reported outcomes and diagnostic interviews were used to identify patients with psychological symptoms and patients with an anxiety or depression disorder, respectively. Previous studies used health insurance data^{17,18} derived from routine care; however, it is known that psychological symptoms and psychiatric disorders often remain undiagnosed among cancer patients³⁷. This may have resulted in an underestimation of the cost difference. Additionally, in the current study, we controlled for sociodemographic and clinical confounders. A potential limitation of this study is the large number of analyses performed. We did not perform a Bonferroni assessment, as different psychological problems were investigated in relation to different types of healthcare use³⁸. Moreover, sample size was too small to conduct multivariate analyses with respect to mental healthcare use. The small number of patients with an anxiety or depression disorder necessitates caution in interpreting the results. Furthermore, it would be interesting to include medication use in the

analysis. Unfortunately, these data are not yet available.

Finally, this study investigated the associations between psychological problems and care use and costs among Dutch cancer patients. Use of care may be limited or driven by health insurance systems³⁹.

Conclusions

HNC patients with psychological problems more often use healthcare and informal care, and have higher costs. This association remained after adjusting for demographic and clinical characteristics, indicating that the association does not result from worse clinical outcomes in patients with psychological problems.

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Appendix

Appendix A and Appendix B are available online at <https://www.mdpi.com/1718-7729/29/5/260>.

Chapter 5

Prevalence of adjustment disorder among cancer patients, and the reach, effectiveness, cost-utility and budget impact of tailored psychological treatment: study protocol of a randomized controlled trial

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Summary

Purpose

Information on the prevalence of adjustment disorders among cancer patients and the value of psychological interventions in this group of patients is limited. This study investigates the prevalence of adjustment disorders among cancer patients as well as the reach, effectiveness, cost-utility and budget impact of a tailored psychological intervention.

Method

This study consists of two parts. Part 1 is an observational study among a representative group of mixed cancer patients after cancer treatment on the prevalence of adjustment disorder as well as the uptake (i.e. reach) of psychological treatment. In Part 2, patients diagnosed with an adjustment disorder are invited to participate in a randomized controlled trial. Patients will be randomized to the intervention (access to the tailored psychological intervention) or control group (waitlist period of 6 months). The psychological intervention consists of three modules: one module containing psycho-education (3 sessions, all patients) and two additional modules (maximum of 6 sessions per module) provided as continuum, in case needed. Module 2 and 3 can consist of several evidence-based interventions (e.g. group interventions, mindfulness, eHealth). The primary outcome is psychological distress (HADS). Secondary outcomes are mental adjustment to cancer (MAC) and health-related quality of life (EORTC QLQ-C30). To assess the cost-utility and budget impact, quality of life (EQ-5D-5L) and costs (iMCQ and iPCQ) will be measured. Measures will be completed at baseline and 3 and 6-months after randomization.

Discussion

This study will provide data of the prevalence of adjustment disorders and the reach, effectiveness, cost-utility and budget impact of a tailored psychological intervention.

Introduction

Worldwide the incidence of cancer is growing. It was estimated that 18.1 million people worldwide were newly diagnosed with cancer in 2018¹. There is convincing empirical evidence that cancer patients have to deal with a wide range of physical symptoms and psychological, social and existential problems related to cancer and its treatment, both during treatment and at (long-term) follow-up. Psychological problems involve symptoms related to anxiety and depression, but also problems with adjustment to cancer and its sequelae². In case of severe and persistent problems with adjustment to cancer, an adjustment disorder can be diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)³. An adjustment disorder is characterized by symptoms such as anxiety, depression or fatigue and can be developed in case of insufficient protective factors (e.g. resilience or meaning making), which can result in significant impairments in a patients' life (e.g. work or study, social relations or emotional problems)³.

Earlier studies showed prevalence rates of adjustment disorder varying from 6% to over 19%, as measured using diagnostic interviews. In a meta-analysis of Mitchell et al. (2011)⁴ the prevalence of adjustment disorder among cancer patients was estimated to be 19%, while in more recent studies somewhat lower prevalence rates of 6% to 17% were reported⁵⁻⁸. In a recent large study in Germany of Mehnert et al. (2014)⁷ in a population of mixed cancer patients who had their cancer diagnosis for on average 13.5 months, 11% of all patients had an adjustment disorder in the previous four weeks (independently of other psychological disorders such as anxiety or depression).

In case an adjustment disorder is diagnosed, evidence or practice based psychological interventions should be available and provided to the patient³. However, in clinical practice, psychological treatment is often not optimally accessible for cancer patients, especially for those with an adjustment disorder. Several bottlenecks in the organization of psychological treatment have been identified, including problems with identifying cancer patients with an adjustment disorder, and problems with referral to psychological treatment⁹⁻¹³. In addition, when an adjustment disorder is diagnosed in cancer patients, the accessibility of psychological care is limited, since there is currently no adequate coverage and reimbursement of adjustment disorders treatments in cancer patients after active cancer treatment¹⁴.

A systematic review of Faller et al. (2013)¹⁵ and several studies published after the conduction of this review¹⁶⁻²⁴ showed evidence for the effectiveness of psychological interventions targeting cancer patients, including self-management interventions, eHealth interventions, group interventions, and individual interventions. Also, two reviews showed that psychological interventions targeting cancer patients are likely

to be cost-effective at potentially acceptable willingness-to-pay thresholds^{25,26}. Three recent cost-utility studies, on meaning-centred group psychotherapy, stepped psychological care, and blended cognitive behavioural therapy, even showed that psychological treatment is more effective and potentially less costly compared to care-as-usual^{16,27,28}. However, to the best of our knowledge, no study specifically focused on the effectiveness, cost-utility and budget impact of psychological interventions in cancer patients with an adjustment disorder.

This randomized controlled trial, therefore, aims to provide insight into the prevalence of an adjustment disorder among cancer patients, and the reach, effectiveness, cost-utility and budget impact of a tailored psychological intervention. The results are relevant to improve care (including accessibility and reimbursement) for cancer patients with an adjustment disorder.

Methods

The methods section of this study protocol is written in accordance with the STROBE statement for cohort studies and CONSORT statement for reporting randomized controlled trials (RCT)^{29,30}.

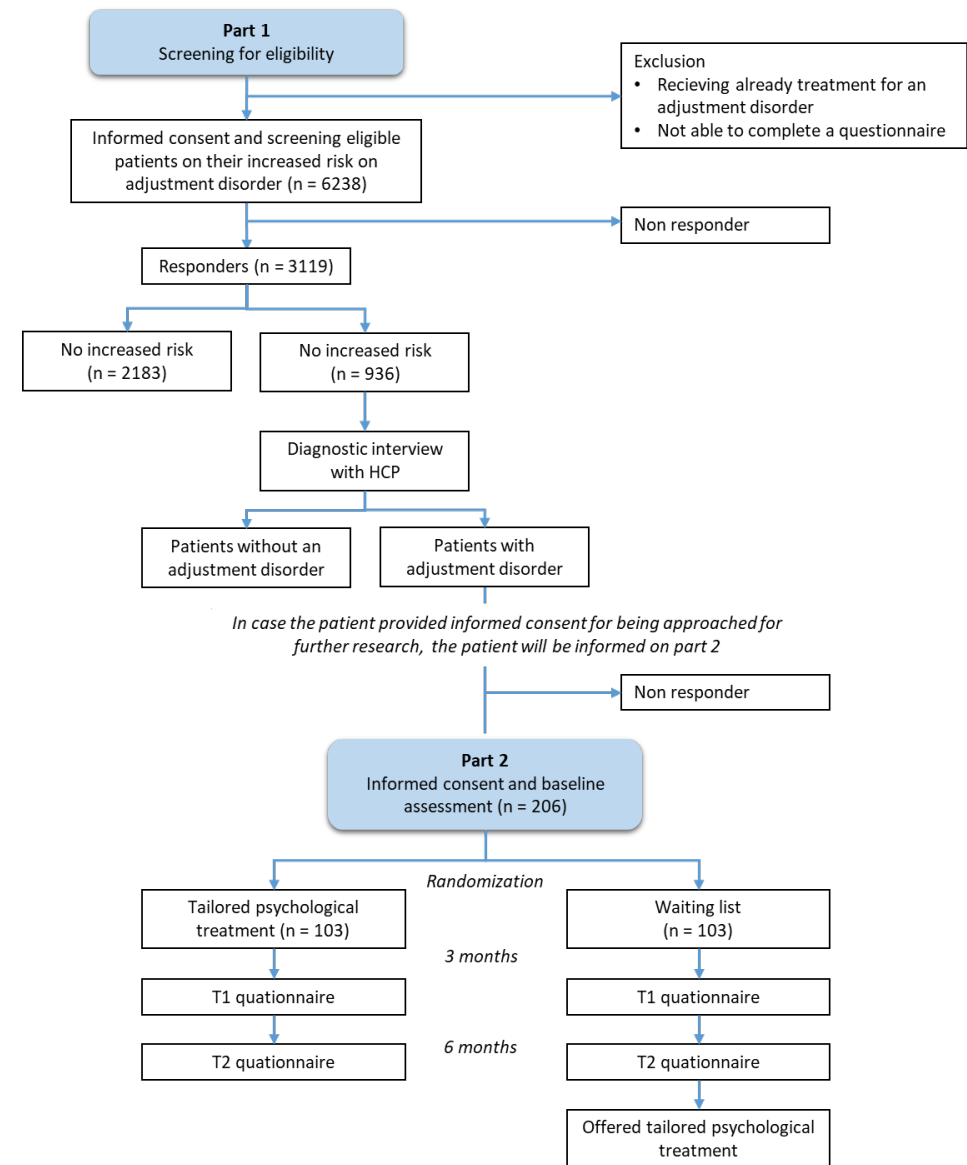
Study design

This study consists of two parts. Part 1 is an observational study among a representative group of cancer patients after medical treatment in which the prevalence of an adjustment disorder as well as the uptake of psychological treatment (i.e. reach) is assessed. Part 2 includes an RCT in which the effectiveness, cost-utility and budget impact of a tailored psychological intervention compared to waitlist control care is investigated. The patient flow through the study is shown in Figure 1 and the schedule of enrolment, assessments and interventions is provided in Figure 2. This study has been approved by the Medical Ethical Committee of the VU University Medical Center.

Part 1: Study population and inclusion procedure

For Part 1 of this study, we aim to screen a representative group of mixed cancer patients on the prevalence of an adjustment disorder. Participants will be included in this study in case they are diagnosed with cancer (all types and stages, except non-melanoma skin cancer) before July 2018, finished cancer treatment with curative or palliative intent (all treatment modalities, except for endocrine therapy in breast/prostate cancer) and are aged ≥ 18 years. A random selection will be drawn by the Netherlands Cancer Registry (NCR) of patients from participating departments of participating hospitals. The NCR registers all newly diagnosed cancer patients within 6 months after diagnosis in the Netherlands.

Figure 1. Study design of Part 1 and 2 combined with expected number of patients per step.



*Healthcare professional (HCP).

The patient information letter will be sent by post to the eligible patient by the former treating physician. When a patient is willing to participate, he or she is asked to provide informed consent. All data will be collected using the Patient Reported Outcomes

Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) system. PROFILES is a registry and is directly linked to data of the NCR. All necessary permissions were obtained to access and use the data and who gave this permission.

Figure 2. Standard Protocol Items as highly Recommended according the SPIRIT.

TIMEPOINT	STUDY PERIOD							
	Enrolment Part 1	Screening	Diagnostic interview	Enrolment Part 2	Allocation	Post-allocation		Close out
	-t _e	t _e	T _{di}	-t ₀	t ₀	t ₁	t ₂	t ₃
ENROLMENT:								
Eligibility screen	X			X				
Informed consent	X			X				
Allocation					X			
INTERVENTIONS:								
Psychological intervention					↔			
Usual care					↔			
Psychological intervention								↔
ASSESSMENTS:								
HADS		X			X	X	X	
DT and problem list		X						
CIS		X						
Adjustment disorder diagnosis			X					
Uptake of treatment			X					
MAC					X	X	X	
EORTC QLQ-C30					X	X	X	
IMCQ					X	X	X	
IPCQ					X	X	X	
EQ-5D-5L					X	X	X	
Sociodemographic parameters		X			X			
Clinical parameters		X			X			

Abbreviations: HADS, Hospital Anxiety and Depression Scale; CIS, Checklist Individual Strength; MAC, Mental Adjustment to Cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; iMCQ, Medical consumption questionnaire; iPCQ, Productivity cost questionnaire; HCP, healthcare professional

Part 1: Prevalence and reach

The prevalence of adjustment disorder diagnosis will be investigated using a two-step approach. First, patients will be screened on the increased risk for an adjustment disorder using a set of screening questionnaires. Patients will be asked to complete these questionnaires online or via paper-and-pencil. The screening questionnaires consist of the distress thermometer (DT), the problem list and the Hospital Anxiety and Depression Scale (HADS). The DT measures the level of distress experienced in the last week on a thermometer ranging from 0 (no distress) to 10 (extreme distress)³¹. The problem list measures 47 different problems, including practical problems, family/social problems, emotional problems, spiritual/religious concerns, physical problems and a free-text section on any additional problems on a dichotomous scale (Yes/No), as well as a single item on wanting to talk to a psychologist, psychotherapist

or psychiatrist. All items refer to 'last week'. The HADS includes 14-items measuring psychological distress(HADS-T), anxiety and depression as further discussed below³². In addition, patients will be asked to complete the Checklist Individual Strength (CIS) and questions on sociodemographic (e.g. marital status, living situation, education level, employment status) and clinical characteristics (e.g. tumour recurrence). The CIS consists of 20 items (7-point Likert scale) on subjective experiences of fatigue, concentration, motivation, and physical activity³³. The CIS which strongly resembles the multidimensional fatigue inventory (MFI)³⁴, has been shown to be a valid and reliable measurement to investigate fatigue with good internal consistency³⁵.

Second, patients with an increased risk for an adjustment disorder (i.e. HADS score >=11, DT >=4 or work/school/study problems, family or social problems, emotional problems, fatigue or wanting to talk to a psychologist or social worker as reported on the problem list) will be invited for a diagnostic interview by a registered psychologist, psychotherapist or psychiatrist trained in clinical care for cancer patients with an adjustment disorder (further called healthcare professional (HCP)). During this diagnostic interview by telephone or face to face the presence of an adjustment disorder will be investigated. HCPs will follow the Dutch guideline on adjustment disorder diagnosis³⁶. The guideline committee recently defined adjustment disorder in patients with cancer as the combination and interaction among three pillars, namely stressors (e.g. cancer diagnosis, fear of cancer recurrence, physical changes in a patients' appearance), insufficient protective factors (e.g. resilience, physical health, meaning, social support, autonomy), and the experience of symptoms (e.g. anxiety, depression, fatigue, relation problems, limited work productivity)³. During the diagnostic interview, the HCP will also complete a form on sociodemographic (age, gender) and clinical (tumour site, stage, phase of cancer (acute/chronic/palliative), time since diagnosis, treatment modality) parameters, and a form on stressors experienced, protective factors, symptoms experienced and actual psychologic diagnosis. To monitor the robustness of this diagnosis, the diagnostic interview will be audio recorded in case the patient provides specific informed consent on this matter. Approximately five percent of the total diagnostic interviews will be scored twice (adjustment disorder yes/no).

Additionally, all participating HCPs will be asked to complete a questionnaire on type of care (primary or secondary care), profession and training, and years of experience in working with cancer patients.

Part 2: Study population and inclusion procedure

Patients diagnosed with an adjustment disorder in Part 1 of this study will be invited to participate in Part 2 (the RCT). Patients will be first introduced to the study by the HCP. The coordinating researcher of the study will further inform interested patients by

phone. Also, the patient information form and informed consent of Part 2 will be sent to the patient. After obtaining informed consent, the patient is asked to fill in the baseline questionnaire via the internet or using paper-and-pencil. After completing the baseline questionnaire, the patient will be randomized into either the intervention group (start of the tailored psychological intervention within 3 a 4 weeks) or the waitlist control group (receive a tailored psychological intervention after a waitlist period of 6 months). All patients will be asked to complete questionnaires before randomization (T0), and 3 (T1) and 6 months (T2) after randomization. In case of non-response to these questionnaires a reminder letter and a paper-and-pencil questionnaire will be sent after 3 weeks. If they do not respond to this reminder, they will be contacted by telephone within 2 weeks. Reasons for dropouts will be registered. Data will be collected using the PROFILES system.

Part 2: Tailored psychological intervention

The psychological intervention investigated in this proposed project follows the Dutch guideline on diagnosis of adjustment disorders³⁶ and consists of 3 modules. Module 1 encompasses a maximum of 3 sessions on psycho-education with an HCP. Module 2 and 3 encompass both a maximum of 6 sessions. Module 2 and 3 can consist of all evidence-based interventions outlined in the guideline on adjustment disorders, such as cognitive behavioural therapy, mindfulness, group interventions, online interventions or pharmacotherapy³. Depending on the wishes and needs of the patient a specific type of therapy per module will be offered to the patient (tailored treatment)³⁷.

After each last session of a module the HCP will assess in accordance with the patient if another module is needed. To support this assessment the patient will complete the HADS during this session, following the guideline on diagnosis of adjustment disorders³⁶. When sufficiently effective, only the short psychological treatment module 1 will be provided. The longer treatments (module 2 or module 3) will only be offered if the previous psychological treatment module was insufficiently effective, so the 3 modules will be provided as a continuum.

Part 2: Control group

Patients randomised to the waitlist control group receive the tailored psychological intervention after a waitlist period of 6 months. This period is comparable with the usual waitlist period for psychological care in the clinical practice. During the waitlist period it is allowed to receive usual care. Usual care received during the study will be measured using the healthcare utilization questionnaire discussed below.

Part 2: Randomization

Randomization will be conducted centrally by an independent person in blocks of

four and six using an automatically created randomisation list. Randomization will be stratified for the patient self-reported prognosis and severity of psychological distress by an independent person. Patients are not blinded to treatment allocation. Data managers will be blinded to the treatment allocation.

Part 2: Outcome assessments

The primary outcome of Part 2 is psychological distress. Secondary outcomes are Mental Adjustment to Cancer and health-related quality of life. In addition, the cost-utility and budget impact of the psychological intervention will be investigated (Table 1). To determine cost-utility and budget impact, Quality-Adjusted Life-Years (QALYs) and costs will be measured. For the cost-utility and budget impact analyses from a societal perspective, intervention costs, healthcare costs, costs of the patient and his/her family (e.g. informal care costs and travel costs) and costs in other sectors (e.g. productivity losses) will be collected. The healthcare perspective will only include intervention costs and healthcare costs and the insurer perspective will only include costs reimbursed by the healthcare insurance company.

Table 1. Outcome measures and used instruments.

Part	Outcome	Outcome measure	Instrument
1	Primary outcome	Reach: prevalence of adjustment disorder (yes/no) and uptake of the tailored psychological intervention (yes/no)	Screening (DT, problem list and HADS) and interview
1	Other collected measurements	Fatigue	CIS
2	Primary outcome	Psychological distress	HADS
2	Secondary outcomes	Mental adjustment to cancer	MAC
		Health-related quality of life	EORTC-QLQ-C30
		Cost-utility measures	
		Medical utilization costs	iMCQ questionnaire
		Informal care costs	iMCQ questionnaire
		Productivity losses	iPCQ questionnaire
		Quality adjusted life-years	EQ-5D-5L
1-2	Other collected measurements	Socio-demographic and clinical characteristics	Study specific questionnaire
		Healthcare professional characteristics	Short questionnaire on type of care

Abbreviations: HADS, Hospital Anxiety and Depression Scale; CIS, Checklist Individual Strength; MAC, Mental Adjustment to Cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; iMCQ, Medical consumption questionnaire; iPCQ, Productivity cost questionnaire; HCP, healthcare professional

Primary outcome measures

Psychological distress will be measured with the HADS. The HADS is a 14-item (4-point Likert scale) patient-reported outcome measure for measuring psychological distress,

anxiety and depression³². All items refer to the last week. The total HADS (HADS-T) score ranges from 0 to 42. A higher score indicates higher levels of distress. The HADS is a valid instrument for use in cancer patients and Dutch persons³⁸.

Secondary outcome measures

Cognitive and behavioural response to cancer diagnosis and treatment will be assessed using the 40-item (4-point Likert scale) Mental Adjustment to Cancer (MAC) questionnaire. The MAC scale comprises five subscales: fighting, spirit, helplessness/hopelessness, anxious preoccupation, fatalism and avoidance³⁹. All items refer to the current situation. A higher score on the subscales indicate more fighting spirit, helplessness/hopelessness, anxious preoccupation, fatalism or more avoidance^{40,41}. Besides, based on these five sum scores, two summary scores can be calculated, namely positive adjustment (17 items) and negative adjustment (16 items). Psychometric characteristics of the MAC have previously been investigated among mixed cancer patients, including Dutch cancer patients⁴¹.

Health-related quality of life will be measured with the 30-item (4-point Likert scale) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30). This questionnaire consists of a global health-related quality of life scale, five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three symptom scales (nausea and vomiting, fatigue and pain) and 6 single items relating to dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties^{42,43}. All scales and single items can be converted to a score from 0 to 100. A higher score on the functioning scales or the global quality of life scale represents a better quality of life, whereas a higher score on the symptom scales or the single items indicate a higher level of symptoms. The EORTC QLQ-C30 is a valid and reliable instrument for health-related quality of life assessments in various cancer populations^{42,43}.

Other outcomes as socio-demographic and clinical parameters and HCP characteristics are similar to the already collected measurements in Part 1 of this study.

Outcome measures on cost-utility and budget impact

Costs will be measured by questionnaires developed by the Institute for Medical Technology Assessments of the Erasmus University Rotterdam, as recommended in the Dutch Health Care Insurance Board (CVZ) guideline⁴⁴. Healthcare utilization (e.g. visits to the general practitioner, visits to the medical specialist, and hospitalization) and received informal care will be assessed with the Medical Consumption Questionnaire (iMCQ)⁴⁵. Losses due to absenteeism and presenteeism (decreased work productivity) will be assessed with the productivity cost questionnaire (iPCQ)⁴⁶. In this study an

adapted version of both questionnaires will be used with a recall period of 3 months.

QALYs will be calculated by multiplying the time spent in a specific health state with the quality (utility) of that health state. Utilities will be measured by using the EuroQol 5-dimensions 5-item (5-point Likert scale) instrument (EQ-5D-5L). The EQ-5D-5L consist of five dimensions of quality of life (mobility, self-care, usual activities, pain/discomfort and anxiety/depression)⁴⁷. The resulting profile of answers can be transformed to a value given by the general public: the EQ-5D index using the Dutch index tariff⁴⁸. A visual analogue scale is also included, which represents the patients' judgment of his own health state on a scale from 0 (worst health state) to 100 (best health state).

Sample size

The sample sizes of Part 1 and 2 depend on each other. To demonstrate an effect size in Part 2 of 5 points on the HADS as statistically significant, anticipating a standard deviation of 11 (i.e. two times the baseline standard deviation of the HADS), 77 participants in each condition are needed at follow-up (power 80%, significance level 5%). Anticipating a drop-out rate of 25% between baseline and 6 month follow-up, 103 participants per condition, thus 206 in total, need to be included at baseline. Estimating a willingness to participate in this RCT of 60%, 343 patients will need to be approached to participate in the RCT in Part 2⁴⁹. Taking into account a prevalence rate of adjustment disorders of 11% as estimated by Mehnert et al.⁷, 3119 cancer patients need to be screened in Part 1 to identify 343 patients with adjustment disorders. Anticipating a response rate of 50%, 6238 patients need to be approached for the screening.

Statistical analysis

In Part 1 and Part 2 quantitative analyses will be performed using the IBM Statistical package for the Social Science (SPSS) version 25 (IBM Corp., Armonk, NY USA) and STATA version 14 Descriptive statistics will be generated for all socio-demographic and clinical characteristics and outcome measures. Chi-square tests, independent t-tests and Mann-Whitney tests (in case of non-normality of the measure) will be used to analyse whether randomization resulted in comparable patient groups. Analyses will be performed according to the intention-to-treat principle. A p-value < 0.05 will be considered significant.

Part 1 aims to investigate the prevalence of having an adjustment disorder, to investigate the uptake of psychological treatment among cancer patients with an adjustment disorder and to investigate its determinants. Determinants of having an adjustment disorder or uptake of psychological care will be entered one-by-one to the logistic regression model using a p-value for entry of 0.05. Potential determinants include scores

on the patient-reported outcomes, socio-demographic, and clinical characteristics of the patient, as well as HCP characteristics. Part 2 aims to investigate the effectiveness of the intervention on the primary outcome measure (HADS) with the use of linear mixed models. The linear mixed model will contain a fixed effect for arm/group, time and their two-way interaction, and a random effect for subject. A significant ($p < 0.05$) two-way interaction indicates a difference in effectiveness between the intervention and the control group. In that case, post-hoc effect sizes, at 3 and 6 months follow-up, will be calculated using Cohen's d .

For the cost-utility analyses, pertinent guidelines will be used⁴⁴. Analyses will be conducted in agreement with the intention-to-treat principle from both a societal and healthcare perspective. Costs will be calculated by multiplying resource use by integral cost prices as presented in the cost guideline⁴⁴. Productivity losses due to absenteeism and presenteeism will be calculated using the friction cost approach. Missing data on costs and utilities will be imputed using multiple imputation. The time horizon will be set at 6 months, and therefore neither costs nor effects need to be discounted. Incremental cost-utility ratios (ICURs) will be calculated with their 95% confidence intervals using 5,000 bootstrap replications, which will be projected on a cost-utility plane. In addition, ICUR acceptability curves will be presented and sensitivity analyses will be performed focusing on uncertainty surrounding most important cost items.

For the budget impact analyses, the current guideline on budget impact analyses of the Dutch National health Care Institute (ZIN) and the International Society for Pharmacoeconomic and Outcomes Research will be used^{44,50}. To perform a budget impact analysis insight is needed on: a) size of the target population, b) costs of the intervention and 3) other costs (such as other healthcare costs). Several budget impact analyses will be performed, as this will provide insight into the uncertainty surrounding the budget impact of providing psychological treatment to patients with cancer with an adjustment disorder. Budget impact analyses will be performed from a healthcare (i.e. including intervention costs and healthcare costs), societal (i.e. including intervention costs, healthcare costs, costs of the patient and his/her family and costs in other sectors) and insurer perspective (i.e. including costs reimbursed by the healthcare insurance company).

Discussion

This paper describes the protocol of a study that aims to provide evidence on the prevalence of an adjustment disorder among cancer patients and the reach, effectiveness, cost-utility and budget impact of tailored psychological treatment.

The first part of this project aims to investigate the prevalence. As mentioned above, previous studies have found prevalence rates varying between 6-19%⁵⁻⁸. However, these studies were heterogeneous in terms of cancer type and methodological quality, warranting further research. Also, the conceptualization of adjustment disorder among cancer patients is poorly studied, which may limit the precision of adjustment disorder diagnosis⁵¹. Most studies used diagnostic interviews to diagnose adjustment disorder⁵⁻⁸. Mehnert et al.⁷, on the other hand, first screened patients on their level of psychological distress using the patient health questionnaire (score of 9 or higher on the PHQ-9), followed by a diagnostic interview in those patients with increased levels of psychological distress. As it is estimated not to be feasible to conduct a diagnostic interview in the more than 3000 patients needed for this study, we will in line with the study of Mehnert et al.⁷ first screen the patients on their risk for having an adjustment diagnosis using patient-reported outcomes measures.

As it is not yet clear which screening questionnaire should be used to preselect patients on their risk for having an adjustment disorder³, we will preselect patients using the DT, problem list and the HADS. Previous studies have investigated the predictive value of the DT⁵²⁻⁵⁴, HADS^{53,55-59}, PHQ-2⁵², Zung Self-rating Depression Scale (ZSDS)⁶⁰ and One Question Interview (OQI)⁵⁴ to identify patients with an adjustment disorder. Most studies, however, have been conducted on the HADS and DT. Three studies that investigated the predictive value of the DT showed that a cut-off ranging between the >3 and >5 resulted in the best screening performance, whereas other studies investigating the HADS found a cut-off ranging between >9 and >15. In our study all patients with an increased risk on the questionnaire (i.e. HADS score ≥ 11 , DT ≥ 4 , certain problems on the problem list or wanting to talk to a psychologist or social worker) will be asked to participate in the diagnostic interview. In line with the study of Mehnert et al.⁽⁷⁾, we expect to find a prevalence rate of adjustment disorder of 11% (independent of other diagnoses).

The second part of this project aims to investigate the effectiveness, cost-utility and budget impact of the tailored psychological intervention. It is expected that this psychological intervention will be especially effective, since the intervention is tailored to the individual needs regarding intensity of the intervention (i.e. number of modules provided) and wishes regarding the type of intervention. Besides being effective, it is hypothesized that offering this intervention will be cost-effective and potentially even cost-saving.

The cost saving potential is related to the design of the study in which patients are first provided with the short psychological treatment (module 1). The following modules (i.e. module 2 and 3) will only be offered to the patient if the previous psychological

treatment module is insufficiently effective. This principle is comparable to a previously investigated stepped care intervention targeting head and neck cancer and lung cancer patients with psychological distress which was shown to be more effective and less costly compared to usual care^{17,27}.

Strengths and limitations

A strength of this study is that its design is in line with clinical practice, as we will investigate a tailored psychological intervention, which may consist of different types of interventions, and not only one specific intervention. Second, this study investigates not only the effectiveness and cost-utility of tailored psychological treatment, but also the prevalence of adjustment disorder and reach of the tailored care. Insight in the prevalence and reach will enable accurate budget impact analysis of providing such psychological treatment to cancer patients with an adjustment disorder. Third, the proposed study will assess the cost-utility and budget impact of the intervention from a healthcare, societal and insurer perspective. So far, the majority of the performed economic evaluations have used the healthcare perspective. However, several guidelines recommend using the societal perspective which includes also for examples productivity losses and informal care costs^{61,62}. This is of importance since these costs have shown to be a great contributor to costs of cancer⁶³. Finally, detailed analysis will be conducted on determinants of the prevalence of an adjustment disorder and the reach of psychological care, which will help to identify possible risk groups in the future.

This study, however, also has some limitations. First, this study includes a short follow-up of 6 months in total, which hampers the possibility to investigate the effectiveness and cost-utility of the intervention on the long term. However, a longer waiting list period was considered as not ethical for the patients. Second, the provided intervention consists of a great diversity of evidence-based interventions. Although this approach follows current routine psychological care, it makes it harder to draw conclusions on the effectiveness of any one specific intervention (e.g. self-management or group therapy). Third, this study targets a heterogeneous study population of mixed cancer patients treated with either curative or palliative treatment, which may limit the ability to draw firm conclusions on the effectiveness of psychological treatment in specific study populations. Fourth, as mentioned above a different method will be used to diagnose adjustment disorder compared to methods used in the previous studies, which makes comparison with previous studies harder. However, to investigate the quality of the diagnostic interviews, these interviews will be checked on robustness by audio recording it.

Implementation and clinical practice

In the Netherlands, psychological treatment for cancer patients undergoing medical

treatment is reimbursed as part of the reimbursement of cancer treatment. Since 2012, however, psychological cancer treatment during follow-up (after active cancer treatment) is no longer reimbursed for cancer patients with an adjustment disorder. To make an evidence-based decision on future reimbursement of psychological treatment targeting cancer patients with an adjustment disorder, the Dutch minister of Health, Welfare and Sport requested this study on the prevalence of adjustment disorders, actual reach, effectiveness, cost-utility and budget impact of psychological treatment for this patients group. If this study will demonstrate that the psychological intervention is effective and cost-effective, further steps need to be taken to support reimbursement and implementation of this program in clinical practice. In addition, guideline committees will be informed and recommended to adapt the guidelines of tailored psychological care for cancer patients with an adjustment disorder.

Conclusion

In conclusion, if the psychological intervention is effective and cost-effective, this study will provide support for the reimbursement of psychological interventions for cancer patients with an adjustment disorder. Consequently, this study may contribute to the implementation and optimization of accessibility of psychological treatment for cancer patients with an adjustment disorder. However, considering a broader perspective, this study may also add important knowledge to the literature of economic evaluations of psychological interventions for cancer patients in general.

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Chapter 6

Adjustment disorder in cancer patients after treatment: prevalence and acceptance of psychological treatment

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Summary

Purpose

To investigate the prevalence of adjustment disorder (AD) among cancer patients and the acceptance of psychological treatment, in relation to sociodemographic, clinical and psychological factors.

Methods

Breast, prostate and head and neck cancer patients of all stages and treatment modalities (N=200) participated in this observational study. Patients completed the Hospital Anxiety and Depression Scale, Checklist Individual Strength, Distress Thermometer and problem list. Patients with increased risk on AD based on these questionnaires were scheduled for a diagnostic interview. Patients diagnosed with AD were invited to participate in a randomized controlled trial on the cost-effectiveness of psychological treatment. Participation in this trial was used as a proxy of acceptance of psychological treatment. Logistic regression analyses were used to investigate associated factors.

Results

The overall prevalence of AD was estimated at 13.1%. Sensitivity analyses showed prevalence rates of AD of 11.5%, 15.0% and 23.5%. Acceptance of psychological treatment was estimated at 65%. AD was associated both with being employed (OR=3.3, CI=1.3–8.4) and having a shorter time since diagnosis (OR=0.3, CI=0.1–0.8).

Conclusions

Taking sensitivity analysis into account the prevalence of AD among cancer patients is estimated at 13% to 15%, and is related to being employed and having a shorter time since diagnosis. The majority of cancer patients with AD accept psychological treatment.

Introduction

Cancer patients may experience psychological problems¹. One of these psychological problems is adjustment disorder (AD). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)² AD occurs when adaptation to a significant identifiable life stressor, such as cancer, fails.

In a meta-analysis of Mitchell et al. (2011)³, the prevalence of AD among cancer patients was estimated at 19.4% (confidence interval (CI) 14.5%-24.8%). More recent studies showed prevalence rates ranging from 6% to 17%⁽⁴⁻⁷⁾. This variability in prevalence rates may result from methodological differences among studies, as well as from different diagnostic procedures for AD. In the Netherlands, a national guideline on AD has been available since 2016, which includes an assessment procedure for AD diagnosis⁸. Another reason for the observed variation may be that prevalence rates differ amongst cancer groups. A study of Mehnert et al.⁴ showed that the prevalence rate of AD varied between tumor types, with the lowest rate of 2.9% in rectal cancer patients and the highest rate of 16.5% in head and neck cancer patients. Other studies demonstrated that patients who were female, more highly educated, diagnosed with a more advanced tumor stage, living in rural areas, and who lacked physical exercise were more frequently diagnosed with AD^{5,9}.

Concerning the usage of psychological treatment, a previous meta-analysis of Brebach et al.¹⁰ showed that 60% of cancer patients exhibiting distress wanted psychological treatment. A higher usage of psychological treatments was associated with a more recent cancer diagnosis, remote compared to face-to-face treatment and psychological treatment provided by a nurse compared to other psychosocial professionals⁹. Other studies showed that patients who were younger, female, and more highly educated were more likely to accept psychological treatment¹¹⁻¹³. However, no study so far has focused on the acceptance of psychological treatment for AD in cancer patients.

In summary, there is inconclusive or limited evidence of the prevalence of AD and the acceptance of psychological treatment for AD among cancer patients, as well as its associated factors. The aim of this study was to investigate 1) the prevalence of AD among cancer patients in relation to sociodemographic and clinical factors, 2) to investigate sociodemographic, clinical and psychological factors associated with AD among cancer patients with an increased risk for AD, and 3) to investigate the acceptance of psychological treatment among patients with AD in relation to sociodemographic, clinical, and psychological factors. Factors associated with AD among cancer patients in general and cancer patients with an increased risk for AD were investigated separately, as patient reported outcome measures (PROMS) are increasingly used in clinical

practice to identify patients with psychological problems. Due to the design of this study, the association between psychological factors and prevalence of AD could only be investigated among patients with an increased risk for AD.

Methods

Design, participants and study procedures

This observational study recruited cancer patients from AmsterdamUMC, Canisius Wilhelmina Hospital and Radboudumc, the Netherlands, between September 2019 and January 2020. The study was part of a randomized controlled trial (RCT) on the effectiveness and cost-utility of tailored psychological treatment targeting cancer patients with AD¹⁴. Patients were included, when they: 1) were diagnosed with cancer (all types and stages, except non-melanoma skin cancer) between July 2004 and July 2019, 2) were aged ≥ 18 years and 3) completed primary cancer treatment with curative or palliative intent (all treatment modalities, except for endocrine therapy in breast and prostate cancer).

Random selections of patients were drawn by the Netherlands Cancer Registry (NCR) which registers all newly diagnosed cancer patients. Recruitment started among breast, prostate, and head and neck cancer patients. Due to the COVID-19 pandemic patients with other cancer diagnoses could not be recruited. The (former) treating physician checked the eligibility of the patients. After confirming eligibility, a patient information letter with informed consent form was sent to the patient by mail. After consenting, the patient was asked to complete the study questionnaire measuring their risk for AD.

Study procedures were approved by the Medical Ethical Committee of VUmc and followed the Dutch Medical Research Involving Human Subjects Act.

Primary outcome

The primary outcomes were prevalence of AD and acceptance of psychological treatment. Prevalence was measured through a two-phase approach including a screening procedure and a diagnostic interview.

Patients were screened on their risk for AD using the Hospital Anxiety and Depression Scale (HADS), Distress Thermometer (DT) and problem list. The HADS is a psychometrically validated 14-item self-report questionnaire that measures symptoms of anxiety (HADS-A) and depression (HADS-D) in the last week. Also, a total HADS (HADS-T) score can be calculated ranging from 0 (no distress) to 42 (severe distress)¹⁵. The DT measures the level of distress experienced in the last week on a scale ranging

from 0 (no distress) to 10 (extreme distress)¹⁶. The problem list measures 47 different problems in the last week, including an item on willingness to talk to an expert, followed by a question on type of expert (psychologist, social worker, dietician, physiotherapist, nurse, peers or other)¹⁶. Increased risk for AD was defined as HADS-total ≥ 11 or DT ≥ 4 or willingness to talk with a psychologist or social worker¹⁴.

Patients with an increased risk for AD were invited for a diagnostic interview either by telephone or face-to-face. The interviews were carried out by trained psychologists, who were registered in the expert database of the Dutch Association for Psycho-oncology (NVPO) or under supervision of a registered psychologist. All psychologists followed an E-Learning program on diagnosis and treatment of AD, which included a reader, videos and an online assessment^{8,17}. The E-learning comprised several learning objectives including the definition of AD among cancer patients and how to describe symptoms along the criteria of the DSM-V). The psychologists completed a form per patient on DSM-V classification of AD (yes/no).

Patients diagnosed with AD were invited by the psychologist to participate in an RCT in which patients received tailored psychological treatment immediately or after a period of 6 months¹⁴. If a patient was interested in the RCT, a researcher gave further information via telephone and an information letter was sent. In the case that a patient did not respond, they were reminded after one week by telephone. Reasons not to participate were reported.

Factors associated with AD and acceptance of psychological treatment

To investigate factors associated with AD and acceptance of psychological treatment, the HADS, DT and problem list, the Checklist Individual Strength (CIS) and questions on sociodemographic and clinical characteristics were used. HADS, DT and problem list are described above. The CIS is a valid and reliable 20-item instrument to measure fatigue, concentration, motivation, and physical activity^{18,19}. A higher score (20-140) indicates a higher level of fatigue.

The socio-demographic questions focused on sex (male/female) age (years), marital status (yes/no) education level (high/low), and employment status (yes/no). Clinical data (tumor stage (I-II/III-IV), treatment (single/multiple treatment), and time since diagnosis (less/more than 5 years after diagnosis) and social economic status (high/middle/low) were obtained from the NCR.

Statistical methods

Quantitative analyses were performed using the IBM Statistical package for the Social Science version 26. Descriptive statistics were generated for all baseline characteristics

and outcome measures. To investigate selective non-response in phase 1 (screening), respondents and non-respondents were compared using independent T-test and Chi-square test. In phase 2 (diagnostic interview), participants (those who completed the interview) and drop-outs (those with an increased risk but who did not complete the interview) were also compared. A p -value <0.05 was considered statistically significant.

To estimate the prevalence of AD among patients, the number of patients diagnosed with AD was divided by the total number of participants that completed the screening survey minus the total number of drop-outs in phase 2. In addition, sensitivity analyses were performed in which drop-outs of phase 2 were a) all expected to have AD, b) partly expected to have AD (the same prevalence as other patients in phase 2) and c) all expected to have no AD. To estimate usage of psychological treatment, the number of patients who agreed to participate in the RCT were divided by the total number of patients diagnosed with AD.

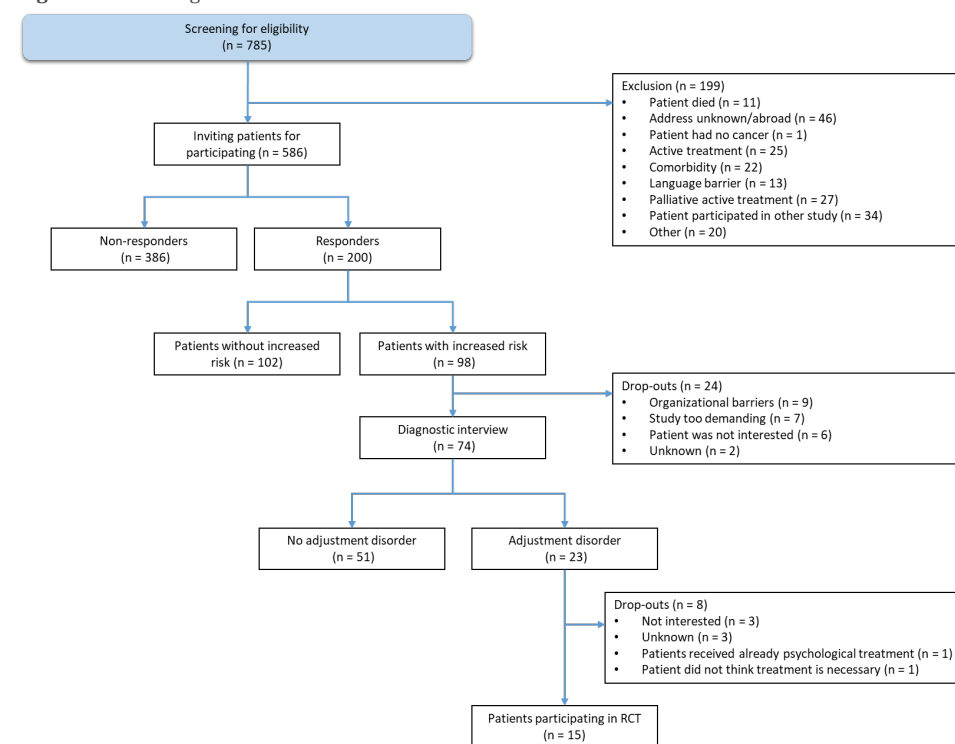
Possible factors associated with 1) the prevalence of AD among all patients and 2) the prevalence of AD among patients with increased risk and 3) the acceptance of a psychological treatment were investigated using forward logistic regression analyses. Variables were entered one-by-one into the logistic regression model using a p -value <0.05 . Since the HADS, DT and problem list were used to identify patients with an increased risk for AD, these variables were not entered in the logistic regression models on the prevalence of AD among all cancer patients.

Results

Participants

Figure 1 shows the study flow diagram. Of the 785 cancer patients who were screened for eligibility, 586 patients were invited to participate in the study. There were significant differences between the patients who responded ($N=200$, 34%) and those who did not respond ($N=386$, 66%). Patients who responded were more often male, had a higher social economic status, were more frequently diagnosed with prostate cancer and more often diagnosed with tumor stage I or II compared to patients who did not respond (Table 1). Characteristics of the study population ($N=200$) are shown in Table 2.

Figure 1. Flow diagram.



Prevalence of AD

Of all 200 patients that completed the survey, 98 patients had an increased risk for AD (49%) and were invited for a diagnostic interview (Figure 1). Of these 98 patients with an increased risk, 74 patients agreed to participate in a diagnostic interview (participation rate 75%). There were no significant differences between participants and drop-outs except that patients who dropped out reported more frequently that they were not willing to talk to an expert (Table 3).

Of the 74 participants with an increased risk for AD and who participated in a diagnostic interview, 23 patients were diagnosed with AD (31%). The overall prevalence rate of AD was estimated at 13.1%. Sensitivity analyses in which the 24 patients who dropped out were all expected to have AD, partly expected to have AD, or all expected to have no AD, showed prevalence rates of 23.5%, 15.0% and 11.5% respectively. Multivariate analysis showed that overall AD was significantly associated with employment status and time since diagnosis (Table 2). The prevalence of AD was higher in patients who were employed (Odds Ratio (OR)=3.3, 95%CI=1.3–8.4) and higher in patients diagnosed less than 5 years ago (OR=0.3, 95%CI=0.1–0.8). Among patients who participated in the diagnostic interview ($N=74$), AD was significantly associated with employment status,

time since diagnosis, and willingness to talk to an expert (Table 2). The prevalence of AD was higher in patients who were employed (OR=3.2, 95%CI=1.3–8.4), patients who were diagnosed less than 5 years prior to the study (OR=0.3, 95%CI=0.007–0.9) and patients who were willing to talk to a psychologist or social worker (OR=9.2, 95%CI=1.9–45.6).

Table 1. Characteristics of responders and non-responders

Characteristics	Non-responders Part 1 (N=386)	Responders Part 1 (N=200)	P-value
Age mean (SD)	68 (10)	68 (10)	0.80
Gender			<0.001
Male	109 (28%)	87 (44%)	
Female	277 (72%)	113 (57%)	
Social economic status			0.002
low	113 (29%)	39 (20%)	
middle	170 (44%)	81 ((41%)	
high	103 (27%)	80 (40%)	
Tumorsite			<0.001
Prostate	49 (13%)	56 (28%)	
Breast	246 (64%)	98 (49%)	
Head and neck	91 (24%)	46 (23%)	
Tumor stage			0.001
I-II	316 (82%)	151 (76%)	
III-IV	69 (18%)	49 (25%)	
Time since diagnosis (years)			0.71
0-5	112 (29%)	53 (27%)	
>5	274 (71%)	146 (73%)	

*abbreviation: SD, standard deviation

Table 2. Characteristics study population.

	Responders (N=200)	Patients without AD (N=153)	Patients with increased risk and no AD (N=51)	Patients with AD (N=23)	Patients with treatment (N=15)	Patient without treatment (N=8)
Age mean (SD)	68 (10)	69 (9)	68 (9)	63 (13)	62 (13)	63 (12)
Gender						
Female	113 (57%)	81 (53%)	27 (53%)	14 (61%)	8 (53%)	6 (75%)
Married (yes/no)						
Yes	136 (68%)	108 (71%)	33 (65%)	13 (57%)	8 (53%)	5 (63%)
Employment status (yes/no)						
Yes	49 (25%)	34 (22%)	8 (16%)	12 (52%)	8 (53%)	3 (38%)
Education (high/low)						
High	115 (58%)	88 (58%)	29 (57%)	12 (52%)	7 (47%)	5 (63%)
Tumorsite						
Prostate	56 (28%)	46 (30%)	10 (20%)	4 (18%)	4 (27%)	2 (25%)
Breast	98 (49%)	71 (46%)	26 (51%)	13 (57%)	7 (47%)	6 (75%)
Head and neck	46 (23%)	36 (24%)	15 (29%)	6 (26%)	4 (27%)	0
Tumor stage (I-II/III-IV)						
III-IV	49 (25%)	38 (25%)	25 (49%)	4 (17%)	3 (20%)	1 (13%)
Treatment ²						
Single treatment	102 (51%)	78 (51%)	26 (51%)	13 (57%)	10 (67%)	3 (38%)
Surgery	76 (38%)	59 (39%)	19 (37%)	10 (44%)	8 (53%)	2 (25%)
Radiotherapy	25 (13%)	18 (12%)	7 (14%)	3 (13%)	2 (13%)	0
Chemotherapy	1 (1%)	1 (1%)	0	0	0	0
Multiple treatment	96 (48%)	73 (48%)	25 (49%)	10 (44%)	5 (33%)	5 (63%)
Surgery+radiotherapy	41 (21%)	35 (23%)	12 (24%)	0	0	0
Surgery+chemotherapy	16 (8%)	10 (7%)	1 (2%)	5 (22%)	1 (7%)	4 (50%)
Radiotherapy+chemotherapy	12 (6%)	9 (6%)	3 (6%)	1 (4%)	1 (7%)	0
Surgery+radiotherapy+chemotherapy	27 (14%)	19 (12%)	9 (18%)	4 (17%)	3 (20%)	1 (13%)
Hormone therapy	60 (30%)	44 (29%)	17 (33%)	12 (52%)	5 (33%)	5 (63%)
Time since diagnosis (years)						
>5	145 (73%)	119 (78%)	40 (78%)	12 (52%)	6 (40%)	6 (75%)
Psychological outcome scores mean (SD)						
HADS-T ²	7.4 (6.9)	5.5 (5.7)	10.8 (6.4)	13.9 (6.9)	14.3 (6.6)	13.3 (7.7)
HADS-A ²	4.1 (3.9)	3.1 (3.3)	7.9 (4.3)	7.9 (4.3)	8.6 (4.5)	6.5 (3.9)
HADS-D ²	3.3 (3.6)	2.5 (3.0)	2.1 (3.9)	6.1 (3.9)	5.7 (3.5)	6.8 (4.6)
DT ²	3.6 (2.8)	2.7 (2.6)	5.7 (6.0)	6.5 (1.9)	6.6 (1.5)	6.4 (2.4)

Table 2. Continued

	Responders (N=200)	Patients without AD (N=153)	Patients with Increased risk and no AD (N=51)	Patients with AD (N=23)	Patients with treatment (N=15)	Patient without treatment (N=8)
CIS ²	58.8 (29.4)	54.6 (25.9)	75.2 (24.4)	81.7 (27.8)	83.6 (26.0)	77.8 (33.0)
Items on problem list (yes)						
Practical problems	71 (36%)	44 (29%)	29 (57%)	13 (57%)	9 (60%)	4 (50%)
Family and social	30 (15%)	17 (11%)	10 (20%)	8 (35%)	5 (33%)	3 (38%)
Emotional	111 (56%)	81 (52%)	41 (80%)	19 (83%)	14 (93%)	5 (63%)
Religious or spiritual	39 (20%)	23 (15%)	12 (24%)	8 (35%)	5 (33%)	3 (38%)
Physical	163 (82%)	117 (77%)	50 (98%)	22 (96%)	14 (93%)	8 (100%)
Willingness to talk to an expert ²						
Yes/maybe	66 (33%)	39 (26%)	25 (49%)	21 (91%)	14 (93%)	7 (88%)

1) Abbreviations: AD, adjustment disorder; CIS, Checklist Individual Strength; DT, distress thermometer; HADS, Hospital Anxiety and Depression Scale; -A, anxiety subscale; -D, depression subscale; -T, Total score

2) Missing data: treatment (2), HADS-T (2), HADS-A (1), HADS-D (1), DT (1), CIS (6), willingness to talk (1)

Table 3. Characteristics of patients with an increased risk for AD who did and did not participate in the diagnostic interview.

	Patients with an increased risk who had an interview in part 2 (N=74)	Drop-outs part 2 (N=24)	P-value
Characteristics			
Age mean (SD)	66 (11)	67 (11)	0.63
Gender			0.09
Female	41 (55%)	18 (75%)	
Married (yes/no)			0.98
Yes	28 (38%)	15 (63%)	
Employed (yes/no)			0.37
Yes	19 (26%)	4 (17%)	
Education (high/low)			0.54
High	41 (55%)	15 (63%)	
Tumorsite			0.85
Prostate	16 (22%)	4 (17%)	
Breast	39 (53%)	14 (58%)	
Head and neck	19 (26%)	6 (25%)	
Tumor stage (I-II/III-IV)			0.64
III-IV	16 (22%)	13 (54%)	
Treatment			0.56
Single treatment	39 (53%)	11 (46%)	
Surgery	29 (39%)	7 (29%)	
Radiotherapy	10 (14%)	4 (17%)	
Chemotherapy	0	0	
Multiple treatment	35 (47%)	13 (54%)	
Surgery + radiotherapy	12 (16%)	6 (25%)	
Surgery + chemotherapy	6 (8%)	1 (4%)	
Radiotherapy + chemotherapy	4 (5%)	2 (8%)	
Surgery + radiotherapy + chemotherapy	13 (18%)	4 (17%)	
Hormone therapy	27 (37%)	6 (25%)	0.30
Time since diagnosis (years)			0.74
>5	52 (70%)	16 (67%)	
Psychological outcome mean (SD)			
HADS-T	11.9 (3.7)	13.0 (7.3)	
HADS-A	6.5 (4.0)	7.0 (3.8)	0.59
HADS-D	5.4 (3.6)	6.0 (4.4)	0.50
DT	5.9 (6.0)	6.1 (1.4)	0.65
CIS	77.6 (25.4)	84.0 (28.2)	0.27
Items on problem list (yes)			
Practical problems	42 (57%)	14 (58%)	0.89
Family and social	18 (24%)	5 (21%)	0.73
Emotional	60 (81%)	20 (83%)	0.80
Religious or spiritual	20 (27%)	8 (33%)	0.55
Physical	72 (97%)	24 (100%)	0.41
Willingness to talk to an expert			
Yes/maybe	46 (62%)	6 (25%)	0.002

Abbreviations: AD, adjustment disorder; CIS, Checklist Individual Strength; DT, distress thermometer; HADS, Hospital Anxiety and Depression Scale; -A, anxiety subscale; -D, depression subscale; -T, Total score; SD, standard deviation

Table 4. Variables associated with AD and acceptance of psychological treatment

Variables	Presence of AD among all patients (N=176)		Presence of AD among patients with increased risk (N=74)		Acceptance of psychological treatment among patients with AD (N=23)	
	Univariate OR [95%CI]	Multivariate OR [95%CI]	Univariate OR [95%CI]	Multivariate OR [95%CI]	Univariate OR [95%CI]	
Clinical and demographic						
Mean age	0.9 [0.9–1.0]		1.0 [0.9–1.0]		1.0 [0.9–1.1]	
Gender (reference = male)	1.4 [0.6–3.9]		1.4 [0.5–3.8]		0.4 [0.1–2.5]	
Marital status (reference = no marital status)	0.5 [0.2–1.3]		0.7 [0.3–1.9]		0.7 [0.1–4.0]	
Employment status (reference = no employment status)	3.2 [1.3–7.9]**	3.4 [1.3–8.5]**	4.9 [1.6–15.0]*	4.4 [1.2–16.0]*	1.9 [0.3–11.0]	
Education (reference = lower)	0.8 [0.3–1.9]		0.8 [0.3–2.2]		0.5 [0.1–3.0]	
Tumor site (reference = prostate)						
Breast	1.4 [0.5–4.0]		0.8 [<0.01 –2.0]		N/A ²	
Head and neck	0.9 [0.2–3.3]		0.4 [0.2–2.8]		N/A ²	
Tumor stage (reference = 1-II)	0.6 [0.2–1.9]		0.6 [0.2–1.9]		1.8 [0.2–20.2]	
Treatment (reference = single)	0.8 [0.3–2.0]		0.8 [0.3–2.2]		0.3 [0.1–1.8]	
Years since diagnosis (reference = 0–5)	0.3 [0.1–0.8]**	0.3 [0.1–0.8]**	0.3 [0.1–0.9]*	0.3 [0.07–0.9]*	0.2 [<0.1 –1.5]	
Psychological outcomes						
HADS-T			1.1 [1.0–1.2]		1.0 [0.9–1.2]	
HADS-A			1.1 [1.0–1.3]		1.1 [0.9–1.4]	
HADS-D			1.1 [0.9–1.2]		0.9 [0.7–1.2]	
DT			1.3 [1.0–1.6]		1.1 [0.7–1.7]	
CIS			1.0 [1.0–1.0]		1.0 [1.0–1.0]	
Items on problem list (reference = no)						
Practical			1.0 [0.4–2.7]		1.5 [0.3–8.4]	
Family and social			2.2 [0.7–6.9]		0.8 [0.1–5.0]	
Emotional			1.2 [0.3–4.2]		8.4 [0.7–100.6]	
Religious or spiritual			1.7 [0.6–5.1]		0.8 [0.1–5.0]	
Physical			0.4 [0.03–7.3]		N/A ²	
Willingness to talk to an expert			10.9 [2.3–51.5]*	9.2 [1.9–45.6]*	2.0 [0.1–37.0]	

1) Abbreviations: AD, adjustment disorder; CIS, Checklist Individual Strength; DT, distress thermometer; HADS, Hospital Anxiety and Depression Scale; -A, anxiety subscale; -D, depression subscale; -T, Total score; OR, odds ratio; CI, Confidence interval

2) Analysis reported with N/A were not applicable due to limited sample size

*P-value<0.05, **P-value<0.01

Acceptance of psychological treatment

Of all 23 patients diagnosed with AD, 15 patients participated in the RCT (65%) (Figure 1). Univariate analysis showed that acceptance of treatment was not significantly associated with any of the investigated factors (Table 2).

Discussion

This study investigated the prevalence of AD among cancer patients and the acceptance of psychological treatment for AD, in relation to sociodemographic, clinical and psychological factors. Overall prevalence rate of AD was estimated at 13%. Being employed and being diagnosed less than five years prior to the study were significantly associated with AD. It was estimated that 65% of patients with AD were willing to accept psychological treatment. None of the investigated factors were associated with acceptance of psychological treatment.

The prevalence rate of AD should be viewed within the light of the sensitivity analyses in which prevalence rates of 24%, 15% and 12% were found. As there were no significant differences in sociodemographic, clinical and psychological characteristics, except from willingness to talk to an expert, between patients with an increased risk for AD who did and did not participate in the diagnostic interview, we assume that scenario b (i.e. prevalence of AD is the same among patients with an increased risk for AD who did and did not participate in the diagnostic interview) is most acceptable. Therefore, a prevalence rate of 13-15% is expected to be most plausible. The prevalence rate of 13-15% is in line with two previous studies reporting prevalence rates of 12%^{4,5}. A previous meta-analysis showed a higher prevalence rate of 19.4%³ and another recent study showed a prevalence rate of 17%⁷. The studies with similar prevalence rates used a comparable two-step method for diagnosing AD as performed in this study, albeit that they used a different screening instrument (PHQ-9)^{4,5}. Such a two-step approach has been proven to be valid and efficient²⁰ and is in accordance with the Dutch guideline on AD⁸. A drawback of this procedure is that patients may have been missed who had a low score on the screening questionnaires who should be diagnosed with AD. This may explain the somewhat higher prevalence rates of 17%⁷ and 19%³ in studies in which all patients received a diagnostic interview. Another explanation may be the absence of clear criteria to diagnose AD, as strict diagnostic criteria for AD in the DSM-V are lacking²¹. As a consequence, the diagnosis of AD may be prone to a psychologist's individual interpretation of the criteria.

The current study demonstrated that being employed, being diagnosed less than five years prior to the study, and willing to talk to an expert are associated with AD,

while sociodemographic factors as age, sex, education, marital status, and clinical factors as cancer type, stage and treatment were not. This is in contrast to previous studies reporting that being female, younger, unmarried, more highly educated, and diagnosed with a more advanced tumor stage are associated with AD^{5,9}. An explanation might be the relatively small sample size of our study that may have failed to detect smaller differences. Also, in our study we included breast cancer, head and neck cancer and prostate cancer patients, whereas previous studies focused on breast cancer patients only or a combination of 13 different tumor types^{5,9}. The distribution of sociodemographic and clinical characteristics such as gender, education level and tumor stage may consequently differ among studies. Another explanation may be that in contrast to our study, in previous studies time since diagnosis and employment status, were not investigated while these factors might be more important than other factors.

Cancer patients who have to manage multiple tasks (e.g. work, housekeeping, children) may perceive cancer-related stressors as a higher burden compared to those with less tasks (e.g. those who are not employed) and therefore may be more vulnerable for developing distress^{22, 23} or psychiatric disorders as AD. Although the association between paid work and AD has not been reported or studied in previous research, it is largely in line with previous research that showed an association between work and psychological symptoms^{24,25}. The same holds for the association between willingness to talk to a psychologist or social worker, which has previously been demonstrated to be associated with higher psychological distress^{16, 26}. The finding that shorter time since diagnosis is associated with AD confirms previous reviews showing that psychiatric disorders as well as psychological symptoms are highest at time since diagnosis and slightly decrease over time^{3,27}. However, there are no longitudinal studies investigating AD over time, so further research is needed to investigate whether AD decreases, increases, or fluctuates over time. Longitudinal research may also clarify whether AD should be regarded as a transient diagnosis or as a disorder that should be treated to prevent a shift to a another type of diagnosis (e.g. depression disorder)^{28, 29}.

Of the 23 patients diagnosed with AD in our study, 65% were willing to participate in an RCT on the effectiveness and cost-utility of psychological treatment for AD, and accepted psychological treatment. This is in line with the results of the meta-analysis of Brebach et al.¹⁰ who found a pooled usage rate of 60% for psychological treatment among cancer patients. Brebach et al.¹⁰ suggested that the possibility of assignment to a non-intervention group, and interventions delivered by telephone compared to face-to-face increased the usage of psychological interventions. A recent qualitative study showed that, from the patient's perspective, the organization of psychological treatment targeting cancer patients should focus on easy accessibility and availability, delivery by specialized psychologists, and integration in medical cancer care. Online

and group therapy are acceptable, but individual face-to-face therapy is preferred³⁰. We did not find factors associated with the acceptance of psychological treatment in the current study, which is possibly due to the limited statistical power. Further quantitative research is needed to investigate factors associated with the acceptance of psychological treatment for AD¹⁰⁻¹².

Study limitations

A strength of our study is the two-step approach to diagnose AD. A limitation is that, due to the COVID-19 pandemic, we had to stop recruiting patients earlier than planned, which resulted in 200 patients with breast, prostate, and head and neck cancer instead of the planned 3000 patients with various types of cancer¹⁴. The low response rate of 34%, and significant differences between the responders and non-responders might also limit the representativeness of this study. Another limitation is that the included patients were comparatively older and time since diagnosis was relatively longer. Finally, the results of this study are applicable to the situation before the COVID-19 pandemic. The prevalence of AD and acceptance of psychological treatment might be different during or after this pandemic. Nevertheless, the findings in this study can serve as benchmark for future studies investigating AD and the acceptance of psychological treatment among cancer patients.

Clinical implications

As the prevalence of AD is substantial and acceptance of psychological treatment is high, implementation of screening procedures to identify patients with AD in routine care is recommended. However, effectiveness and cost-effectiveness of psychological treatment of AD remain to be answered. An ongoing RCT will provide more evidence⁽¹⁴⁾. Further research should also focus on barriers to accept psychological treatment among cancer patients with AD as there is still a large gap between patients who may need treatment and patients who actually accept and use psychological treatment.

Conclusion

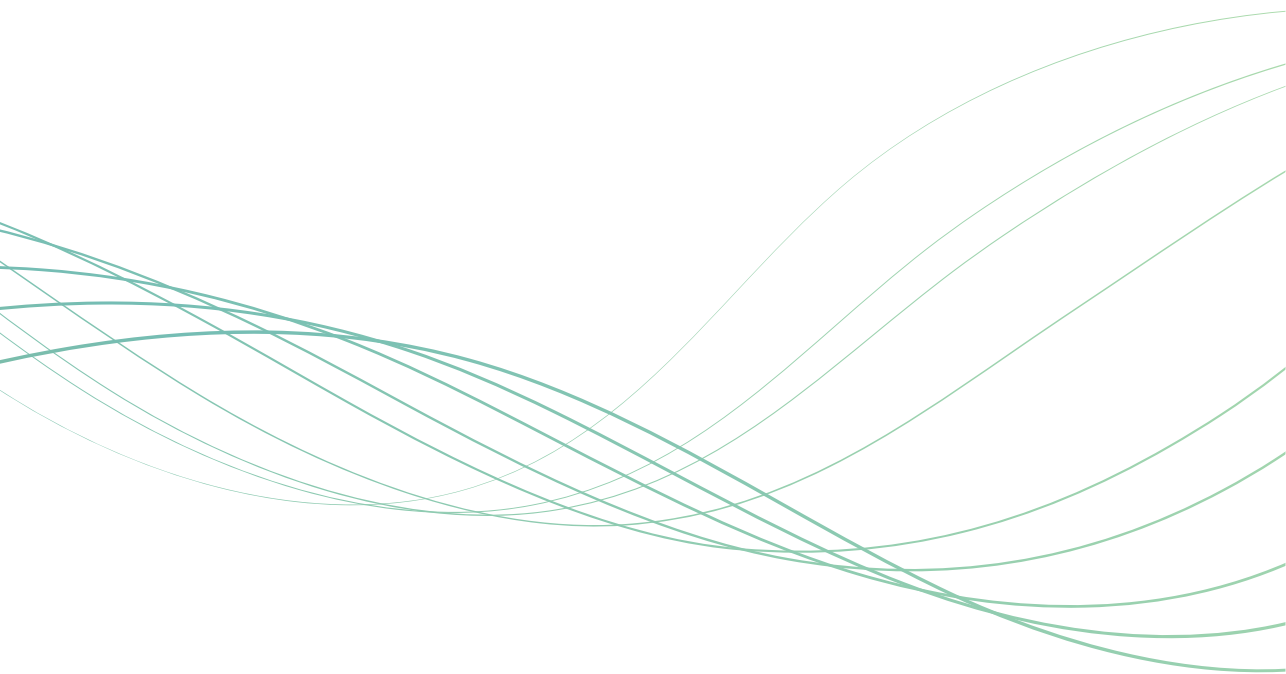
The prevalence of AD among cancer patients is estimated at 13% to 15%. AD among all cancer patients was found to be significantly associated with being employed and shorter time since diagnosis. AD among cancer patients who participated in the diagnostic interview was found to be significantly associated with being employed, shorter time since diagnosis and willingness to talk to an expert. The majority of cancer patients with AD accept psychological treatment.

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Chapter 7

General discussion



General discussion

The main aim of this thesis was to provide insight in psychological problems among cancer patients from a clinical and economic perspective. In this chapter, the main findings of the thesis are discussed and put into perspective compared to current knowledge and clinical practice of psycho-oncology care. Both strengths and limitations of this thesis are presented. Lastly, this chapter presents the implications for clinical practice, recommendations for further research and a conclusion.

Summary of the main findings

A systematic review was conducted of studies investigating psychological problems in relation to healthcare utilization (i.e. mental healthcare, supportive non-mental healthcare, primary care, oncology-related visits healthcare, inpatient healthcare, outpatient healthcare and medication), economic losses by patients and family, economic losses in other sectors (e.g. lost work productivity) and costs in monetary units (**Chapter 2**). With respect to healthcare use, strong evidence was found that patients with fear of cancer recurrence more often use primary care. Patients diagnosed with an anxiety or depression disorder make more use of inpatient and outpatient healthcare. Furthermore, there was strong evidence that patients with symptoms of anxiety or symptoms of depression are less likely to return-to-work. With respect to costs in monetary units, patients with a depression disorder have higher inpatient healthcare costs and outpatient healthcare costs. Patients with an anxiety disorder have higher inpatient healthcare costs. Evidence on all other 80 associations between psychological problems and economic consequences was inconclusive due to limited or no evidence or contrary results. Overall, it can be concluded that psychological problems in cancer patients are associated with increased healthcare use, healthcare costs and delayed return to work. Detailed insight into (associations between) psychological problems and healthcare use and costs over time is lacking, especially among high risk groups as head and neck cancer (HNC) patients.

In **Chapter 3**, the course of symptoms of anxiety and depression and its associated factors up to 2 years follow-up was investigated among 345 HNC patients. This study showed that before treatment 28% of HNC patients experienced symptoms of anxiety and 15% experienced symptoms of depression. Prevalence rates of symptoms of anxiety and depression diminished over time during the first year after treatment. Prevalence of symptoms of depression increased again to 16% at 24-months follow-up. Symptoms of anxiety declined steadily to 10% at 24-months follow-up. The course of symptoms of anxiety from baseline up to 24-months follow-up was significantly associated with age,

pain, problems with social contact and feeling ill, as measured at baseline. The course of symptoms of depression was significantly associated with chemotherapy, worse emotional functioning, speech problems and weight loss, as measured at baseline. Six months after treatment, chemotherapy, worse cognitive and social functioning, insomnia, swallowing problems and trouble with social eating were associated with the course of anxiety from 6-months to 24-months follow-up, while nausea/vomiting, dyspnea, coughing, and feeling ill were associated with the course of depression from 6 to 24-months follow-up. **Chapter 4** described a longitudinal study investigating associations between psychological problems and healthcare and informal care use and costs from time of diagnosis up to two years after treatment among 558 HNC patients. Results demonstrated that both psychological symptoms and psychiatric disorders were associated with more healthcare usage (i.e. primary healthcare and supportive care), informal care use and total costs.

A study protocol was developed to investigate the prevalence of adjustment disorder and the uptake, effectiveness and cost-utility of psychological treatment of adjustment disorder among mixed cancer patients (**Chapter 5**). **Chapter 6** describes the results on the prevalence of adjustment disorder and the uptake of psychological treatment. In a study sample of 200 breast, HNC and prostate cancer patients, prevalence rate of adjustment disorder was estimated at 13% to 15%. Being employed and shorter time since diagnosis were significantly associated with the presence of an adjustment disorder. The majority of the patients diagnosed with adjustment disorder (65%) was willing to receive psychological treatment.

Psychological problems from a clinical perspective

The value of screening

In the past 30 years, the negative impact of cancer and its treatment on psychological well-being has been increasingly recognized¹. To identify cancer patients who might have psychological problems, the term distress was introduced due to its multidimensional construct². Several guidelines have recommended the implementation of psychological distress screening in cancer patients and researchers have developed several validated distress screening tools (e.g. Distress Thermometer (DT), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ))^{3,4}. Many of these short instruments are effective in identifying cancer patients with clinically significant levels of distress and symptoms of anxiety and depression⁴⁻⁶.

In the Netherlands, a guideline on detecting psychosocial distress in cancer patients was developed and effort was undertaken to implement this guideline in clinical

practice, which is still ongoing⁷. More recently, a guideline on adjustment disorder was developed and implementation has started⁸. In both guidelines, it is recommended to use a screening questionnaire to identify patients that might need referral to psychological or psychiatric treatment. In **Chapter 3**, we used the HADS to monitor symptoms of anxiety and depression over time among HNC patients. In **Chapter 6**, as recommended in the Dutch guideline on adjustment disorder, we used two screening questionnaires to identify patients at risk for an adjustment disorder among a mixed cancer population. In case patients scored above the cut-off score (i.e. HADS-total ≥ 11 or DT ≥ 4 or willingness to talk psychologist or social worker), they were invited for a diagnostic interview to establish an adjustment disorder.

The prevalence and course of symptoms

Based on the results in **Chapter 3 and 6**, it can be concluded that psychological problems are common among cancer patients and seem to decrease over time for symptoms of anxiety, and to fluctuate over time for symptoms of depression. Although the study on adjustment disorder was cross-sectional, based on the underrepresentation of patients at long-term follow-up among those with an adjustment disorder, it seems that the prevalence of adjustment disorder may also decrease over time. These findings are in line with a meta-analytical review on psychological problems among cancer patients. Based on 58 studies from 1980 to 1994, psychological problems gradually diminished over time, with a significant improvement in anxiety and a non-significant improvement in depression⁹. More recent systematic reviews reported that psychiatric disorders as well as psychological symptoms are highest at time of diagnosis and slightly decrease over time^{10,11}. In contrast, there are also studies among breast cancer (follow-up 0-5 year after diagnosis) and colorectal (follow-up 0-1 year after diagnosis) populations which showed that psychological symptoms fluctuate over time, suggesting that psychological problems may be transient^{12,13}.

Also, a recent study¹⁴, found a substantial impact of the COVID-19 pandemic on the prevalence of adjustment disorder in cancer patients, which dropped from the 13-15% before the COVID-19 pandemic to 3% during the COVID-19 pandemic. This prevalence rate was based on different criteria compared to the study described in **Chapter 6**. The criteria were changed from “HADS-total ≥ 11 or DT ≥ 4 and willingness to talk with a psychologist or social worker” into “HADS-total ≥ 11 or DT ≥ 4 and willingness to talk with a psychologist or social worker”. This change was made because we learned from the study described in **Chapter 6** that many patients who were not willing to talk to a psychologist or social worker were most often not diagnosed with AD and/or were not interested to psychological treatment (i.e. participation in the RCT). Based on these new criteria, the prevalence rate of adjustment disorder before the COVID-19 pandemic was recalculated as 10% (n=200) which is still much higher than the prevalence rate

of 3% during the COVID-19 pandemic. The main reason for this difference seems to be that less patients were willing to talk to psychologist or social worker during the COVID-19 pandemic.

Dekker et al. (2017)¹⁵, argued to reconsider the conceptualization of psychological distress for empirical and theoretical reasons. Currently the approach of screening is based on the assumption that low scores on screening tools are better (i.e. ‘less is better’). Dekker et al.¹⁵ implied that using cut-off scores may not be valid as some patients with high scores may experience emotional responses, which may actually facilitate coping with cancer^{16,17}. Dekker et al.¹⁵ introduced the concept of adaptive emotional responses and maladaptive emotional responses instead of using cut-off scores to frame a ‘good’ or ‘bad’ response to cancer and its treatment. However, how to define an emotional response as adaptive or maladaptive remains unclear. This relates to the problem that it is not yet understood whether an adjustment disorder should be regarded as transient or as a disorder that should be treated to prevent a shift to another (worse) type of diagnosis such as a depression or anxiety disorder^{18,19}. Bai (2021)²⁰ stated that it is unclear under which circumstances transient psychological problems may reflect normal response rather than a problematic response.

As found in this thesis (**Chapter 3 and 6**), there are several factors associated with psychological problems in cancer patients, such as younger age, shorter time since diagnosis, being treated with chemotherapy, being employed, several physical symptoms such as pain, nausea/vomiting, dyspnea, coughing, feeling ill, weight loss, speech and swallowing problems, insomnia, cognitive problems, as well as worse psychosocial functioning such as worse emotional functioning and problems with social contacts. There seems to be an inherent difference on the co-occurrence of symptoms dependent on symptom severity²¹. A previous study showed there was more clustering of these physical and psychosocial symptoms among cancer survivors with severe physical and psychosocial outcomes, compared to survivors with less severe outcomes, in which separate clusters of physical and psychosocial symptoms were found. These findings indicate that screening for psychological problems should go hand-in-hand with screening for physical and social problems. Moreover, patient’s resilience should be taken into account, which may protect a patient from developing psychological problems after the diagnosis and treatment of cancer^{22,23}. In the current clinical interviews for diagnosing adjustment disorder this is already taken into account²⁴. This biopsychosocial profiling of patients may help to understand why part of cancer patients with psychological problems do not accept psychological treatment.

Uptake of psychological treatment

In this thesis, the uptake of psychological treatment was estimated at 65% among

patients with adjustment disorder (**Chapter 6**). The systematic review of Brebach et al. (2016)²⁵ reported a 60% uptake for psychological treatment for patients with symptoms of distress, anxiety and depression. The psychological intervention for adjustment disorder investigated in this thesis consisted of three modules. The first module consisted of 4 sessions for diagnosis and psycho-education. Module 2 and 3 consisted of a variety of evidence-based interventions (e.g. group interventions, mindfulness, eHealth). These two additional modules were provided as continuum, in case needed. Psychological interventions with a stepped care-oriented approach have the potential to improve the uptake and efficiency of cancer care.

Comparable to the psychological intervention for adjustment disorder investigated in this thesis, a previous stepped care program targeting cancer patients with psychological problems also investigated tailored psychological treatment. This stepped care program comprised four steps: step 1) a period of 2 weeks of watchful waiting, step 2) guided self-help, step 3) a nurse-led problem solving intervention and step 4) psychological or psychiatric treatment. Each next step was only provided in case symptoms did not resolve and a care coordinator controls whether a patient received the right treatment. A randomized controlled trial (RCT) revealed that among 265 lung cancer or HNC survivors (out of 1298 screened for psychological problems (HADS) (prevalence rate 20%), the uptake of this stepped care program was 59%²⁶. Of the patients in the intervention group, 30% spontaneously recovered after a period of two weeks of watchful waiting. In contrast to this stepped care study, an RCT among advanced colorectal cancer patients with psychological problems, showed that the uptake of a stepped care program was only 26% (of which approximately half used only watchful waiting)²⁷. In the latter study, the study population was very vulnerably (and 20% died during the study), which might explain the differences in study uptake. Another explanation might be that palliative care is better organized and easier accessible than cancer survivorship care²⁷.

Although tailored psychological treatment has thus the potential to improve the uptake of psychological treatments, literature seems to suggest that even with easy accessible care a group of cancer patients with psychological problems is not accepting psychological treatment²⁸. An explanation may be that this group of patients includes the patients with clustered physical problems. As psychological problems may have occurred due to physical complaints, psychological interventions may be less attractive to patients. However, a study about the uptake of psychological treatment in HNC patients showed the opposite as patients with speech problems and oral pain were more often willing to receive psychological treatment compared to patients without. Brebach et al.²⁵, on the other hand showed that patients with more distress do not accept psychological treatment. Furthermore, it may be, as suggested by Dekker et al.⁽¹⁵⁾,

that these are patients with an adaptive emotional response. So, it should be noted, that not all patients may benefit from and accept psychological treatment and there is still a challenge in screening and offering suitable care for these unmet needs.

Psychological problems from an economic perspective

Carlson and Bultz²⁹ previously suggested that cancer patients with psychological problems may not only have increased mental healthcare use but also make more use of other healthcare domains. In 2018 a systematic review revealed that psychological problems among a mixed group of cancer patients were associated with higher healthcare costs among cancer patients in the US³⁰. **Chapter 2 and 4** further investigated this association by focusing on psychological symptoms (i.e. distress, symptoms of anxiety, symptoms of depression and fear of cancer recurrence) and psychiatric disorders in relation to economic consequences. Results of **Chapter 2 and 4** support the hypothesis of Carlson and Bultz²⁹ that patients with psychological symptoms and psychiatric disorders not only make more use of mental healthcare, but also of other healthcare domains such as general practitioner visits and inpatients and outpatient healthcare. In addition, patients with psychological symptoms or disorders are less likely to return to work and make more use of informal care.

As it seems logical that patients with an overall worse clinical health status make more use of healthcare, the analysis in **Chapter 4**, was adjusted for potential confounding factors at baseline such as cancer stage, treatment modalities and comorbidity. Even after correction, several associations remained significant indicating that the association between psychological problems and healthcare use and costs does not entirely result from worse clinical health status at baseline. One explanation, as previously hypothesized by Carlson and Bultz²⁹, may be that patients with psychological problems have more difficulties with maintaining a healthy lifestyle and/or are less likely to adhere to treatment recommendations. This may result over time in an overall decreased health status which in turn may result in increased healthcare use and costs. Another explanation may be that cancer patients with psychological problems such as anxiety and fear of cancer recurrence may need more reassurance for their health status (e.g. assurance that their cancer is in remission), resulting in more visits to their healthcare providers. However, the question remains whether physical problems induce psychological problems or it may be the reverse, or that the association is both ways.

The positive association of psychological problems in relation to costs found in this thesis are of importance to consider when building a business case for dissemination and implementation of screening tools and psychological treatment. Efforts to reduce

barriers (e.g. adequate reimbursement of mental healthcare, screening and referral of patients who may need psychological treatment and reducing stigma of psychological problems) to mental healthcare are needed. Supported by this thesis, optimization of psycho-oncology treatment has the potential to impact quality of life and cancer care outcomes in this population, while at the same time reducing healthcare utilization and costs. Several psychological interventions targeting cancer patients suffering from psychological problems have previously been shown to be effective and cost-effective³¹. Among HNC patients a stepped care intervention targeting psychological distress was even found to be effective and cost saving.^{32,33}

Reimbursement

As healthcare costs are rising it is of particular importance to investigate the relation between health outcomes and healthcare costs, and the cost-effectiveness of treatment. Since 2012 there is no adequate coverage and reimbursement of psychological treatment of cancer patients with an adjustment disorder after finishing active cancer treatment in the Netherlands. Results of this thesis are relevant to improve psychological care targeting cancer patients (including accessibility and reimbursement). In the Netherlands the healthcare insurance is organized by 'diagnosis and treatment combination' (DBC) which are used in all hospitals and in mental healthcare. All performances that are reimbursed by the insurance company are expressed in so-called DBC (or DOT) healthcare products. Psychological problems during the treatment phase of cancer can be reimbursed as part of the DBC. However, after active treatment the DBC will be closed and psychological treatment for patients is not reimbursed as part of cancer care anymore. In case the patient needs psychological treatment after active cancer treatment, the patient can receive help from the general practitioner/practice assistant or specialized mental healthcare. For reimbursement of specialized mental healthcare with GGZ-DBC, however, several conditions must be met. The diagnosis adjustment disorder did not meet these conditions and specialized mental healthcare for adjustment disorder is since 2012 not reimbursed in the Netherlands. Nevertheless, starting in 2022 this system will be renewed and reimbursement will be driven by a new concept 'burden of care' instead of GGZ-DBC. Consequently the mental health diagnosis of the patient is of less importance for reimbursement and the need for care is the basis⁽³⁴⁾. Whether the benefits of the new system will actually be in favor of the patients has yet to be revealed.

Strengths and limitations

A strength of this thesis is that it focused on different psychological symptoms and psychiatric disorders as well as different domains of healthcare and societal costs.

Furthermore, this thesis included not only healthcare costs but also societal costs. Besides healthcare use (and costs), also lost work productivity (costs) and informal care (costs) were investigated in this thesis. The analyses from a societal perspective are recommended in several guidelines, including the Dutch manual for healthcare cost.^{35,36} Also, the designs of the included studies are a strength of this thesis. In **Chapter 5** a two-step approach (screening and diagnostic interview) was used to diagnose adjustment disorder in cancer patients instead of a self-report questionnaire only and in **Chapter 3 and 4** a longitudinal study design of 2 years follow-up among a relative large group of 345 and 558 HNC patients respectively was used. Finally, a strength of this thesis is the sound methodology used to perform the analyses. In **Chapter 3**, for example, mixed model analyses were used for analyzing the data, which enables the inclusion of patients with missing data at follow-up. In **Chapter 4** missing data was addressed using multiple imputation and in **Chapter 5** missing data was addressed by conducting sensitivity analyses. Lastly, in **Chapter 4**, bootstrapping was performed to provide insight into the uncertainty surrounding the findings on cost differences.

The studies presented in this thesis are also subject to some limitations. In **Chapter 2**, no meta-analysis was performed because the studies included in the systematic review were very heterogeneous in study population, psychological problems, and cost categories investigated, as well as measurement instruments. Instead, an overview was provided on all economic consequences investigated worldwide in relation to psychological problems among cancer patients and a summarized direction of an association was formulated instead of a conclusion on the magnitude of the association.

Furthermore, in **Chapter 3** it was unknown whether patients received psychological treatment during this longitudinal study and therefore we were unable to control for possible effects of psychological treatment on the course of symptoms of anxiety and depression. Also, in **Chapter 6**, due to the COVID-19 pandemic, we had to stop recruitment of patients earlier than planned, which resulted in 200 patients with breast, prostate, and HNC instead of the planned 3000 patients with various types of cancer. In addition, the study sample was not representative for the entire breast, prostate and HNC population with regard to gender, social economic status, tumor site and tumor stage, which hampers generalizability. The same holds for **Chapter 4**, in which the study sample was not representative for the HNC population with regard to living status, tumor stage, performance state and comorbidity. Another limitation is that the Dutch guideline was used to define economic outcome categories in **Chapter 2 and 4**. However, this framework may not be suitable for all countries, as in some countries healthcare costs are paid directly by the patient (without healthcare insurance). In those countries healthcare resource use may need to be categorized as 'economic losses by patients' instead of the category on 'healthcare use'. Also, the type

of healthcare insurance system may influence the results on healthcare use, as patients may be limited or driven to use healthcare based on their insurance status³⁷.

Finally, in this thesis the term “psychological problems” was used to cover distress, symptoms of anxiety, symptoms of depression, fear of cancer recurrence, anxiety disorder, depression disorder and adjustment disorder. However, it is debatable whether it is appropriate to include psychiatric disorders and psychological symptoms under the same denominator “psychological problems”. Furthermore, we did not include psychological symptoms such cognitive functioning and limited our studies to above mentioned categories.

Clinical implications and future research

Based on the results of this thesis, some recommendations and directions for future research can be given. First, the findings support the hypothesis that cancer patients with psychological problems make more use of healthcare and informal care besides mental healthcare use only. In the systematic review there were 94 associations to investigate, but for many of them (85%) evidence was inconclusive or limited. In chapter 4 we investigated several of these associations on which evidence was inconclusive or lacking (e.g. informal care use). However, as still many of the associations are understudied and chapter 4 focused specifically on HNC patients, it would be interesting to further investigate these associations. Especially, insights are needed with respect to the relation between psychological problems and informal care use and lost work productivity. Also, further research is called for the pathway between psychological problems and healthcare utilization and costs and covariates as this is not yet understood.

Secondly, this thesis showed that the presence of psychological problems often changes over time. Further research should shed light on the understanding when psychological symptoms reflect normal response rather than a risk for a psychiatric disorder. Further research should also shed a light on the difference between a ‘normal emotional response’ and a ‘mal-adaptive emotional response’ in which case professional help is needed. As there is still a large gap between patients who may need treatment and patients who actually accept and use psychological treatment, this research question may also help understanding the gap between patients with psychological problems and patients who accept psychological treatment.

Thirdly, this thesis provided evidence on the prevalence of adjustment disorder and the uptake of psychological treatment for patients with adjustment disorder. However,

evidence on the effectiveness, cost-utility and budget impact of psychological treatment for adjustment disorder is still lacking. This thesis already described the study protocol and the RCT is ongoing. However, results should be analyzed in the future to provide insights. Based on current evidence derived from this thesis, the yearly number of cancer patients that needs and accepts psychological treatment for adjustment disorder is estimated on 12,650 to 17,250.

Conclusion

Prevalence of psychological problems in cancer patients varies over time in the first two years after a cancer diagnosis. Symptoms of anxiety and symptoms of depression range between 10-28% and 7-16%, respectively. Prevalence of adjustment disorder is estimated at 15% at most. It is estimated that approximately two-third of patients with psychological problems accepts psychological treatment.

Several factors were found to be associated with psychological problems in cancer patients, such as younger age, shorter time since diagnosis, being treated with chemotherapy, being employed, several physical symptoms including pain, nausea/vomiting, dyspnea, coughing, feeling ill, weight loss, speech and swallowing problems, insomnia, cognitive problems, as well as worse psychosocial functioning including worse emotional functioning and problems with social contacts.

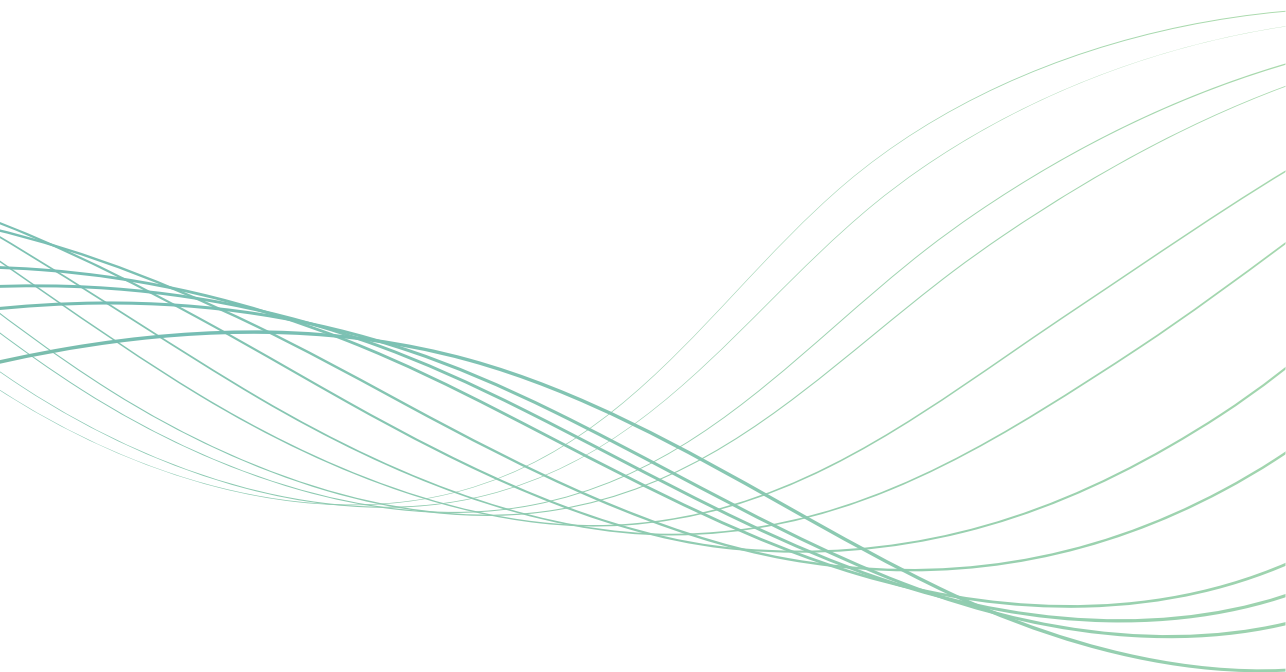
Finally, psychological problems were found to be associated with higher healthcare use and costs, delayed return to work, and more informal care use. The findings of this thesis indicate that reimbursement of psychological interventions for cancer patients with psychological problems have the potential to improve the quality of life of cancer patients, but also to reduce burden to the healthcare system by lowering healthcare and societal costs.

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Addendum

Summary
Samenvatting
Acknowledgement
About the author



Summary

Chapter 1 presents the general introduction of the thesis. First, general background information is given about the psychological impact of cancer and its treatment. Special attention is paid to head and neck (HNC) cancer patients as studies have shown that HNC patients reported one of the highest prevalence rates of mental comorbidity among all cancer types. Secondly, existing evidence of psychological problems among cancer patients are described. Psychological problems, in this thesis, are defined as: distress, symptoms of anxiety, symptoms of depression or fear of cancer recurrence (further called psychological symptoms) and anxiety disorder, depression disorder or adjustment disorder (further called psychiatric disorder). Subsequently, the economic impact of cancer and the relation of economic consequences and psychological problems in cancer patients is introduced. After providing the already existing knowledge, research gaps are presented. The main aim of this thesis is to provide insight in psychological problems among cancer patients from a clinical as well economic perspective.

Chapter 2 provide a systematic review on the association of psychological problems with healthcare and societal resource use and costs among cancer patients. PubMed, PsycINFO, and Embase were used for the search and identified 4157 records. In total, 49 articles were included (psychological symptoms (n = 34), psychiatric disorders (n = 14), both (n = 1)) which focused on healthcare use (n = 36), economic losses by patients and family (n = 5), economic losses in other sectors (n = 8) and/or costs (n = 13). Results showed that psychological symptoms and psychiatric disorders were positively associated with increased healthcare use (mental, primary, inpatient, outpatient healthcare), losses in other sectors (absence from work), and costs (inpatient, outpatient, total healthcare costs). Moderate evidence was found for a positive association between (any) psychiatric disorder and depression disorder with inpatient healthcare and medication use, respectively.

Chapter 3 further explored the association between psychological problems and healthcare and informal care use and total costs in head and neck cancer patients, taking into account the main research gaps identified by the systematic review. Data were used of 558 patients of the NET-QUBIC study. Anxiety and depression disorder (Composite International Diagnostic Interview (CIDI)), distress, symptoms of anxiety and depression (HADS) and FCR (Cancer Worry Scale (CWS)) were measured at baseline and 12-months follow-up. Care use and costs were measured at baseline, 3-, 6-, 12- and 24-months follow-up. Results showed that distress, symptoms of anxiety or depression, FCR, and/or anxiety disorder at baseline were significantly associated with higher use of primary care, supportive care and/or informal care. Symptoms of anxiety, FCR, and/or depression disorder at 12-months follow-up were significantly associated with use

of primary care, supportive care and/or informal care. Distress, symptoms of anxiety and FCR at baseline were associated with higher total costs. **Chapter 3** suggests that patients with psychological problems make more use of healthcare and informal care and have higher costs which is not the result of worse clinical outcomes.

Chapter 4 aimed to investigate the course of symptoms of anxiety and depression from diagnosis up to 2 years follow-up and its associated factors among head and neck cancer patients. Data were used of the NETHERLANDS Quality of Life and Biomedical Cohort study (NET-QUBIC). In total, 345 patients completed questionnaires on anxiety and depression (Hospital Anxiety and Depression Scale, (HADS)), health-related quality of life and symptoms (EORTC QLQ-C30/QLQ-H&N35) before treatment, and 6-weeks, 3-, 6-12-, 18-, and 24-months after treatment. Increased risk for anxiety (HADS-anxiety > 7) was 28.7% among patients before treatment, which declined to 10.0% at 24-months. Increased risk for depression (HADS-depression > 7) was 15.1% before treatment, 18.2% at 3-months, 7.2% at 12-months and 16.0% at 24-months. Factors associated with a worse course of anxiety and depression were younger age, treatment with chemotherapy, worse HRQOL and higher symptom burden.

Chapter 5 presents the study protocol for investigating the prevalence of adjustment disorders (AS) among cancer patients as well as the reach, effectiveness, cost-utility and budget impact of a tailored psychological intervention for AS. The study consisted of two parts. Part 1 was an observational study among mixed cancer patients on the prevalence of AS as well as the acceptance of psychological treatment for AS. In Part 2, patients diagnosed with an adjustment disorder were invited to participate in a randomized controlled trial RCT. Patients will be randomized to the intervention (access to the tailored psychological intervention) or control group (waitlist period of 6 months). The primary outcome is psychological distress (HADS). Secondary outcomes are mental adjustment to cancer (MAC) and health-related quality of life (EORTC QLQ-C30). To assess the cost-utility and budget impact, quality of life (EQ-5D-5L) and costs (iMCQ and iPCQ) were measured. Measures were completed at baseline and 3 and 6-months after randomization.

Chapter 6 presents the results of the first part of the study described in Chapter 5. In total, 200 breast, prostate, and HNC patients of all stages and treatment modalities participated in the study. First, patients completed the HADS, Distress Thermometer and Problem list. Patients with an increased risk based on these questionnaires were invited for a diagnostic interview. In case a patient was diagnosed with AS, they were invited for an RCT on the (cost-)effectiveness of psychological treatment. Participation in this trial was used as a proxy of acceptance of psychological treatment. Results showed that the prevalence was estimated at 13% to 15% and was related to being

employed and having a shorter time since diagnosis. The acceptance of psychological treatment was estimated at 65%.

Chapter 7 provides a general discussion of the thesis, in which the main findings of the thesis are demonstrated and discussed. It also includes strengths and limitation, clinical implications and recommendations for further research. This thesis demonstrated that psychological problems in cancer patients are common and varies over time. Psychological problems were associated with several clinical and demographic factors. It was estimated that approximately two-third of patients with psychological problems accepts psychological treatment. Also, psychological problems were found to be associated with higher healthcare use and costs, delayed return to work, and more informal care use. The findings of this thesis indicate that reimbursement of psychological interventions for cancer patients with psychological problems have the potential to improve the quality of life of cancer patients, but also to reduce burden to the healthcare system by lowering healthcare and societal costs.

Samenvatting

Hoofdstuk 1 omvat een algemene inleiding van het proefschrift. Allereerst wordt de psychologische impact bij patiënten met kanker globaal beschreven. Hierbij wordt specifiek ingegaan op de psychologische gevolgen bij patiënten met hoofd-hals kanker, aangezien dit een specifieke populatie is waar psychologische problemen vaak worden gerapporteerd. Ten tweede, wordt de definitie 'psychologische problemen' verder uitgewerkt. In dit proefschrift is er voor gekozen om onderzoek te doen naar distress, symptomen van angst, symptomen van depressie, angst voor terugkeer van kanker, depressieve stoornis, angst stoornis en een aanpassingsstoornis. In dit proefschrift wordt daarnaast onderscheid gemaakt tussen psychische symptomen en psychiatrische stoornissen, waarbij deze tezamen als 'psychologische problemen' worden benoemd in dit proefschrift. Vervolgens wordt de economische impact van deze psychologische klachten geïntroduceerd. Voor het maken van maatschappelijke keuzes met betrekking tot het leveren en vergoeden van psychische zorg is het van belang dat zowel het klinische aspect als het economische aspect wordt meegenomen in onderzoeken. Na het beschrijven van de bestaande literatuur zal er ingegaan worden op onderzoeksvragen die in dit proefschrift worden behandeld. Het doel van dit proefschrift is om meer inzicht te geven in psychologische klachten bij patiënten met kanker en welke economische gevolgen hiermee samen hangen.

In **hoofdstuk 2** wordt er aan de hand van een systematisch literatuur studie onderzoek gedaan naar de associatie tussen psychische problemen bij patiënten met kanker en de economische impact hiervan. Het doel van dit onderzoek was om een richting van de associaties te vinden en niet de sterkte van de associatie. In dit onderzoek zijn 49 studies geïncludeerd (psychologische symptomen (n = 34), psychiatrische stoornissen (n = 14), beide (n = 1)) die focuste op 1), kosten in de gezondheidszorg (n = 36), 2) kosten van familie en vrienden (n = 5), 3) kosten in andere sectoren (n = 8) en/of 4) kosten expliciet uitgedrukt in geld (n = 13). In totaal zijn er 94 associaties onderzocht waarbij er bij 14 associaties een significant verband werd gevonden. Resultaten lieten zien dat er sterk bewijs was dat psychologische symptomen en psychiatrische stoornissen waren geassocieerd met meer zorggebruik (psychologische zorg, eerstelijnszorg, en intramurale en poliklinisch zorg), kosten in andere sectoren (afwezigheid van werk) en hogere kosten uitgedrukt in geld (intramurale en poliklinisch zorg en totale zorgkosten). Meer onderzoek is nodig naar psychische problemen in relatie met informeel zorggebruik en productiviteitsverliezen op werk.

Hoofdstuk 3 bevat een longitudinale studie waarbij het beloop van symptomen van angst en depressie van baseline tot 2 jaar na baseline en geassocieerde factoren werd onderzocht bij patiënten met hoofd-hals kanker. In totaal vulden 345 patiënten vragenlijsten in over angst en depressie (Hospital Anxiety and Depression Scale, (HADS)), kwaliteit van leven en symptomen gerelateerd aan hoofd-hals kanker op baseline, en 6

weken en 3, 6, 12, en 24 maanden na behandeling. Resultaten lieten zien symptomen van angst en depressie vaak voorkomen bij patiënten met hoofd-hals kanker. Symptomen van angst kwamen voor bij 29% van de patiënten vóór de behandeling wat geleidelijk daalde tot 10% op 24 maanden na de behandeling. Symptomen van depressie kwam voor bij 15% van de patiënten vóór behandeling, bij 18% op 3 maanden, 7% op 12 maanden en 16% op 24 maanden na behandeling. Factoren die samenhangen met een slechter beloop van angst en depressie waren een jongere leeftijd, behandeling met chemotherapie, slechtere kwaliteit van leven en een hogere symptomlast.

In **hoofdstuk 4** wordt de relatie tussen psychische problemen en zorggebruik, informeel zorggebruik en totale kosten in patiënten met hoofd-hals kanker onderzocht. De data van 558 patiënten uit de NET-QUBIC studie werd hiervoor gebruikt. Angst en depressieve stoornis werden gemeten met een diagnostisch interview (Composite International Diagnostic Interview (CIDI)) en distress, symptomen van angst, symptomen van depressie (HADS) en angst voor terugkeer van kanker (Cancer Worry Scale (CWS)) werden gemeten met vragenlijsten op baseline en 12 maanden na behandeling. Zorggebruik en kosten werden gemeten op baseline en 3, 6, 12 en 24 maanden na behandeling. Resultaten lieten zien dat stress, symptomen van angst of depressie, angst voor terugkeer van kanker en/of een angststoornis gemeten op baseline significant geassocieerd waren met meer eerstelijnszorg, ondersteunende zorg en informele zorg. Symptomen van angst, angst voor terugkeer van kanker en een depressieve stoornis gemeten op 12 maanden na baseline waren significant geassocieerd met eerstelijnszorg, ondersteunende zorg en informeel zorggebruik. distress, symptomen van angst, angst voor terugkeer van kanker gemeten op baseline waren geassocieerd met hogere totale kosten. **Hoofdstuk 4** demonstreert dat patiënten met psychologische problemen meer gebruik maken van (informele) zorg en hogere kosten maken dan patiënten zonder psychische problemen en dat dit verschil niet het resultaat is van slechte klinische gezondheid op baseline.

Hoofdstuk 5 beschrijft het studieprotocol van het ADJUST project waarin onderzocht wordt wat de prevalentie van aanpassingsstoornissen bij patiënten met kanker is, evenals wat het bereik, de effectiviteit, de kostenutiliteit en de budgetimpact van een psychologische interventie op maat is. Dit onderzoek bestaat uit twee delen. Deel 1 is een observationeel onderzoek naar de prevalentie van een aanpassingsstoornis en wie er gebruik maken van psychologische behandelingen. In deel 2 worden patiënten met een aanpassingsstoornis uitgenodigd om deel te nemen aan een randomized controlled trial (RCT) (n=206). Patiënten worden gerandomiseerd in de interventie groep (direct toegang tot een op maat gemaakte psychologische interventie) of controlegroep (toegang na 6 maanden naar een psychologische behandeling). De primaire uitkomstmaat was psychische distress (HADS). Secundaire uitkomstmaten zijn aanpassingsvermogen aan kanker en kwaliteit van leven. Om de kostenutiliteit

en budgetimpact te beoordelen worden kwaliteit van leven en kosten (Medical Consumption Questionnaire (iMCQ), productivity cost questionnaire (iPCQ) gemeten. De vragenlijsten worden afgenomen voor randomisatie en 3 en 6 maanden na randomisatie.

Hoofdstuk 6 presenteert vervolgens de resultaten van het eerste deel van het studieprotocol. In totaal namen 200 patiënten met borst, prostaat of hoofd-hals kanker van verschillende stages en behandel methodes mee aan de studie. Allereerst vulde de deelnemers een vragenlijst in met de HADS, lastmeter en de probleemlijst. Deelnemers met een verhoogd risico werden uitgenodigd voor het diagnostisch interview waarbij een aanpassingsstoornis wel/niet werd vastgesteld. Vervolgens werden deelnemers met een aanpassingsstoornis uitgenodigd voor een RCT naar de (kosten)effectiviteit van de psychologische behandeling voor aanpassingsstoornis als een maat voor het bereik van de behandeling. Resultaten lieten zien dat de prevalentie van aanpassingsstoornis werd geschat op 13% tot 15% waarbij 65% van de deelnemers gebruik wilde maken van de psychologische behandeling.

De algemene discussie, **Hoofdstuk 7**, vat de belangrijkste bevindingen van dit proefschrift samen. Daarnaast worden sterke punten en beperkingen, implicaties, aanbevelingen voor vervolgonderzoek en de conclusie beschreven. Dit proefschrift toonde aan dat psychische problemen veel voorkomen bij patiënten met kanker en dat dit over tijd fluctueert. Naar schatting accepteert ongeveer twee derde van de patiënten met psychische problemen een psychologische behandeling. Daarnaast bleken psychische problemen samen te hangen met meer zorggebruik en -kosten, meer mantelzorggebruik en een langere tijd voor terugkeer naar werk. De bevindingen van dit proefschrift ondersteunen dat vergoeden van psychologische interventies voor patiënten met kanker en psychische problemen het potentieel heeft om de kwaliteit van leven van patiënten met kanker te verbeteren, maar ook om de last voor het zorgsysteem te verminderen door de kosten voor de gezondheidszorg en de samenleving te verlagen.

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“Each of us can make a difference. Together we make change.”

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About the author

Florie van Beek was born in 1995 in Vleuten-de Meern, The Netherlands. After graduating from secondary education in 2013 she started with the Bachelor Health Sciences at VU Amsterdam. She continued with the Master Health Sciences with a specialization in Health Policy. She obtained her degree in 2018. Since 2018 she worked as Junior researcher at the Faculty of Behavioural and Movement Sciences, Department of Clinical, Neuro & Developmental Psychology at the VU Amsterdam. In 2019 this position was expanded to a PhD position in which she managed the ADJUST-study and wrote her thesis.



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