Screening and Diagnosing Adjustment Disorder after Cancer Diagnosis and Treatment

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Chapter 1

General Introduction

Adjusting to cancer and its treatment

World-wide, the incidence of cancer is increasing, leading up to 19.3 million new cases in 2020 (Ferlay J, 2020). Medical treatment for cancer with curative intent is successful for a substantial proportion of patients resulting in an increasing survival rate (Ferlay J, 2020; Sung et al., 2021). Also, an increasing number of patients with advanced cancer are living long term on systemic treatment (Kolsteren et al., 2022). Therefore, more patients have to deal with cancer, the treatment and its consequences. These consequences can result in limitations, pain, problems in sexual functioning, restricted social participation and decreased psychological functioning (Armes et al., 2009; Bai, 2022; Firkins et al., 2020; Kolsteren et al., 2022; Mols et al., 2005; Stein et al., 2008). Adjustment to a disease like cancer can be manifested across multiple life domains like physical, interpersonal, psychological (cognitive, emotional, and behavioural) and social domains. The tasks that are needed to adapt over time may depend on disease severity, prognosis and aggravation and may vary across patients dealing with different personal contexts (Stanton et al., 2007).

An adverse event like a cancer diagnosis or cancer treatment can evoke a large variety of psychological responses (Burney, 2019; Stein et al., 2008). Research reports positive responses like posttraumatic growth (Updegraff & Taylor, 2000), benefit finding (Affleck & Tennen, 1996) and cognitive adaptation (Taylor, 1983), resulting in for example enhanced sense or appreciation of life, more meaningful relationships, or a richer existential and spiritual life (Bonanno, 2004; Menger et al., 2021; Trevino et al., 2016).

On the other hand, research also reports negative responses in a substantial proportion of patients with cancer, for example fear of cancer recurrence (Simard et al., 2013), symptoms of anxiety (Curran et al., 2017), symptoms of depression (Krebber et al., 2014) and distress (Bultz & Carlson, 2006; Riba et al., 2019). Distress is one of the most commonly observed negative responses in the context of cancer (Mehnert et al., 2018), with prevalence rates for high levels of distress between 23% and 52% (Herschbach et al., 2020; Mehnert et al., 2018; Mitchell, 2007; Zabora et al., 2001). Distress is described as "a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioural, emotional), social, spiritual, and/or physical nature that may interfere with one's ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis.". It is recommended by the National Comprehensive Cancer Network to screen for

distress (National Comprehensive Cancer Network, 2019), as early detection and treatment of significant distress can lead to better adherence to cancer treatment and avoiding the development of severe anxiety or depression (Riba et al., 2019). In clinical practice, patients are identified as a possible case of high distress if they score above a cut-off, for example on the Distress Thermometer (Riba et al., 2019) or the Hospital Anxiety and Depression Scale (Vodermaier & Millman, 2011).

High distress scores perse may not be a maladaptive reaction to a potential stressful life-event like cancer diagnosis and treatment and could be considered a normal stress reaction (Bachem & Casey, 2018; Dekker et al., 2020). However, if a major stressful event (stressor) occurs and a person responds with significant distress that is out of proportion to the severity or intensity of the stressor, this distress could fit the psychiatric criteria of the Adjustment Disorder (AD) (American Psychiatric Association, 2013).

Adjustment Disorder definition

The AD definition is documented in the two world's largest classification standard references: the International Classification of Diseases (ICD), a health statistics coding tool describing human conditions (World Health Organization, 2019), and the Diagnostic and Statistical Manual of Mental Disorder (DSM), a facilitator for reliable diagnosis of mental disorders and to provide an official nomenclature for clinicians and researchers (American Psychiatric Association, 2013). In this thesis, the latest edition classification (IDC-11 and DSM-5) of the AD definition have been used and clarified.

The ICD-11 has formulated five criteria for AD: 1. Presence of an identifiable psychosocial stressor(s), symptoms emerge within 1 month of the stressor; 2. Preoccupation related to the stressor or its consequences in the form of at least one of the following: (a) excessive worry about the stressor, (b) recurrent and distressing thoughts about the stressor, (c) constant rumination about the implications of the stressor; 3. Failure to adapt to the stressor that causes significant impairment in personal, family, social, educational, occupational or other important areas of functioning; 4. Symptoms are not of a sufficient specificity or severity to justify diagnosis of another mental or behavioural disorder; 5. Symptoms typically resolve within 6 months, unless the stressor persists for a longer duration (World Health Organization, 2019).

The DSM-5 has described AD with five diagnostic criteria: A. The development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s); B. These symptoms or behaviours are clinically significant, as evidenced by (1) marked distress that is out of proportion to the severity or intensity of the stressor, taking into account the external context and the cultural factors that might influence symptom severity and presentation, and/or (2) significant impairment in social, occupational, or other important areas of functioning; C. The stress-related disturbance does not meet the criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder; D. The symptoms do not represent normal bereavement; E. Once the stressor or its consequences have terminated, the symptoms do not persist for more than an additional 6 months. Subtypes of the AD diagnosis are also included: with depressed mood, with anxiety, with mixed anxiety and depressed mood, with disturbance of conduct, with mixed disturbance of emotions and conduct and unspecified (American Psychiatric Association, 2013). In the Netherlands, it is common to use DSM-5 diagnoses in psychological and psychiatric practices, as reimbursement is related to an established DSM-5 diagnosis by a qualified and registered psychologist, psychiatrist, psychotherapist or physician.

The ICD-11 and DSM-5 diagnoses of AD have many similarities. For both, a stressor and no other mental disorder must be present and both describe that symptoms of AD resolve within six months unless the stressor (or its consequences) persists. Also, distress and functional impairments are key components. The definition of the AD diagnosis differs between the manuals in the onset of the symptoms (1 month vs. 3 months) and that symptoms of distress are more specifically described in the ICD-11 (preoccupation, rumination, excessive worry and/or recurrent distressing thoughts). Furthermore, the combination of distress and significant impairments is not obligatory in the DSM-5 criteria, although this does apply for ICD-11 (O'Donnell et al., 2019).

Since the addition of the AD definition to the ICD and DSM, the definition of AD has been topic of discussion for several reasons. The definition of AD was judged to be problematic because of constraints between the fit of the vague criteria and clinical practice (Reed et al., 2011). Also the distinction between AD and normal stress reactions is unclear and the criticism was that common problems encountered in life are being medicalised (Fabrega & Mezzich, 1987). This is also highlighted by the DSM-5: "*When bad things happen, most people get upset. This is not an adjustment disorder. The diagnosis should only be made when the magnitude of the distress (e.g., alterations in mood, anxiety, or conduct) exceeds what would normally be expected*

(which may vary in different cultures) or when the adverse event precipitates functional impairment.". AD has also been described to have overlap with (subthreshold manifestations of) other mental disorders like post-traumatic stress disorder or depression disorder (Semprini et al., 2010; Stein et al., 2013), or those not meeting the criteria for other disorders, were assigned with an AD (Fard et al., 1978). These comments advocate for further research investigating the manifestation of AD after the occurrence of a major stressor.

Adjustment Disorder: time-limited or persistent?

Criterion E of the DSM-5 AD definition states that symptoms of AD do not persist for more than an additional 6 months once the stressor or its consequences have terminated (American Psychiatric Association, 2013). This implies that by definition AD is a time-limited condition. However, the DSM-5 also states that "*If the stressor or its consequences persist, the adjustment disorder may also continue to be present and become the persistent form*" (American Psychiatric Association, 2013). This significant nuance of the description of AD implies that this time limitation could be interpreted not as strictly as formulated in Criterion E. In the context of cancer, the question can be raised whether being diagnosed with cancer is a single stressor, or that having cancer is accompanied by multiple stressors with multiple consequences (Hund et al., 2016), especially because cancer treatment varies from a minor surgical procedure to months of chemotherapy or life-long systemic treatment. Whether AD is time-limited, or can be of persistent nature, or both, has been stated in literature by Carta et al. using the terminology 'acute adjustment disorder' and 'chronic adjustment disorder' (Carta et al., 2009). To our knowledge, this terminology is not commonly used in research, and no study investigated if this distinction between these two forms of AD is indeed observed in practice. It is important to clarify this issue for clinical implications, as symptoms may resolve spontaneously or may be persistent and hindering and warranting psychological treatment (Bachem & Casey, 2018). As definitions of these two forms of AD are missing, this thesis uses 'time-limited AD' as the form of AD in which AD does not persist more than 6 months, and 'persistent AD' for AD persisting longer than 6 months.

Assessment of Adjustment Disorder: screening and diagnosing

Screening for symptoms of AD in patients treated for cancer can be more beneficial and efficient to identify possible cases without burdening clinicians and patients with time-consuming clinical interviews. The self-report assessment ADNM-20 (and the condensed forms ADNM-8 and ADNM-4) has been developed to meet the need for fast, structured identification of symptoms of AD (Casey, 2014) . The International Adjustment Disorder Questionnaire (IADQ) was developed by other researchers to fill in gaps in the construct of the ADNM-20 that had been risen due to adaptations in the latest ICD-11 edition (Shevlin et al., 2020). Both instruments measure symptoms of AD independent of the nature of the involved stressor, and rarely have been used in cancer research. These recent developments underline that the methodology to screen for AD is still under construction, and no generally accepted gold-standard has been established yet (Bachem & Casey, 2018). In this thesis, the Hospital Anxiety and Depression Scale (HADS) (Spinhoven et al., 1997) serves as a screening questionnaire for symptoms of AD (Ozalp et al., 2008). It screens for emotional distress with symptoms of depression and/or anxiety in line with the AD criteria (American Psychiatric Association, 2013), is validated in cancer survivors (Vodermaier & Millman, 2011) and is commonly used in clinical care.

A diagnostic module for AD is not included in the widely used Clinical Interview Schedule (CIS) (Lewis et al., 1992) or the Composite International Diagnostic Interview (CIDI) (Kessler & Ustun, 2004), and the Scheduled Clinical Interview for DSM-5 (SCID) (First, 2014) and the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) incorporated only a few items relating to AD in an addendum. To fill the gap on adequate diagnostic measures for AD, the Dutch guideline *Adjustment disorder in patients with cancer* (Trimbos-Institute, 2016) was developed to provide psycho-oncological professionals with guidelines to amongst others diagnose AD in the context of cancer. The diagnostic interview that is part of the guideline has not yet been investigated on diagnostic accuracy and validity.

The prevalence of AD in cancer populations received little attention in research (Zelviene & Kazlauskas, 2018). Two large studies investigated the prevalence of AD following cancer. A four-week AD prevalence in 11.1% of patients was found across major tumour entities (Mehnert et al., 2014) using an oncology-specific adaptation of the CIDI with supplementary questions according to DSM-IV criteria for AD. In palliative care settings and in oncological and haematological settings respectively,

an AD prevalence of 15.4% and 19.4% was found based on both DSM and ICD definitions (Mitchell et al., 2011).

Sociodemographic, medical and psychosocial factors associated with Adjustment Disorder

Explanation and interpretation of factors associated with AD is important, as the AD diagnosis itself depends on the context of the individual's environmental setting (Criterion B), as '*… symptoms or behaviors are clinically significant…taking into account the external context and the cultural factors that might influence symptom severity and presentation.' (American Psychiatric Association, 2013)*. The DSM-5 also describes that '*… Individuals from disadvantaged life circumstances experience a high rate of stressors and may be at increased risk for adjustment disorders*'. A couple of studies investigated factors related to AD in the context of cancer. A small but significant positive association between AD and female gender was found in a meta-analysis of 24 interview-based studies including 4007 individuals in palliative settings (Mitchell et al., 2011). Being female, higher education and having metastases predicted AD in a study investigating adult patients with cancer (N=2141) from acute care hospitals, outpatient cancer facilities, and cancer rehabilitation clinics in Germany (Hund et al., 2016). In male and female patients with cancer seeking psycho-oncological help (N=566), significant risk factors for AD were low-income level, cancer recurrence and history of psychiatric disorder (Anuk et al., 2019). Due to the large diversity in sample characteristics and study designs, more research is needed to expand the knowledge on associated factors relevant for AD in patients treated for cancer.

Adjustment Disorder and the accessibility to psychological treatment

Psychological problems (Burney, 2019) and psychiatric disorders (Mitchell et al., 2011) are prevalent among patients with cancer. One of the most frequently identified domains of unmet needs is the psychological domain (Mirosevic et al., 2019). In the Netherlands, the accessibility to psychological treatment for patients treated for cancer was limited due to reimbursement reformations in the health care system in 2012. Financial reimbursement was granted based on a (DSM-5) diagnosis with a diagnostic code. Psychological treatment for AD was excluded for reimbursement, mainly due to the high declaration costs of a treatment trajectory for an AD diagnosis.

Patients and professionals, supported by the *Netherlands Comprehensive Cancer Organisation* ('Integraal Kankercentrum Nederland') advocated for reintroducing reimbursement of psychological treatment for AD related to cancer. By order of the Ministry of Health, Welfare and Sport a report was published advising to improve psychosocial care for patients with a major somatic condition like cancer. A guideline *Adjustment disorder in patients with cancer* ('Richtlijn aanpassingsstoornis bij patiënten met kanker') was developed focussing on prevention, screening and diagnostics, treatment and organisation of care. Additionally, a scientific project (the ADJUST-project) was set up to investigate the prevalence of AD in patients treated for cancer and to investigate the effectiveness, cost-utility and budget impact of tailored psychological treatment for AD in these patients (van Beek et al., 2019). The rationale and findings of the ADJUST project as well as previously collected data (Custers et al., 2017) will be used in this thesis to investigate screening and diagnosing AD in patients and cancer survivors.

Aims and outline of the thesis

Summarizing the evidence as outlined in this Introduction, little is known about the course of symptoms of AD, the AD prevalence and themes relevant for an AD diagnosis after a cancer diagnosis. Data will be used of observational cross-sectional and longitudinal studies in several cancer populations with various tumour types, and varying time since cancer diagnosis and cancer treatment. We aim to provide an extensive perspective on the screening and diagnosing of AD with quantitative and qualitative research. The aims are to:

1) Investigate the presence and course of symptoms of AD over time in with patients with breast cancer and colorectal cancer;
2) Investigate the prevalence of AD in patients with mixed tumour types;
3) Investigate the themes relevant in a diagnostic interview for AD in patients with cancer.

In **Chapter 2**, we will investigate symptoms of AD occurring in women up to five years after breast cancer treatment. Until now, the prevalence of AD after cancer had been investigated cross-sectionally in a few studies, and we are especially interested how symptoms of AD develop over time, using a longitudinal design. We will investigate the occurrence of time-limited and persistent symptoms of AD and their associated factors after colorectal cancer diagnosis in **Chapter 3**. As a cancer

diagnosis is assumed to be the stressor related to the development of symptoms of AD, men and women will be observed directly after receiving a cancer diagnosis.

The prevalence of AD and uptake of psychological treatment will be investigated in **Chapter 4**. This study focusses on AD in the Dutch population treated for cancer over the last 15 years using the diagnostic interview part of the Dutch guideline *Adjustment disorder in patients with cancer*. This diagnostic interview was developed based on expert opinion and scientific evidence and is not yet evaluated scientifically. Therefore, we will additionally investigate the interrater agreement and adherence to the interview manual to describe the quality of the conducted diagnostic interviews (**Chapter 5**). This chapter also qualitatively elaborates on the relevant themes expressed by participants and professionals when AD is diagnosed.

Lastly, **Chapter 6** includes a general discussion of the studies described in this thesis and provides clinical implications and recommendations for future research. This chapter is completed by an overall conclusion.

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Chapter 2

Trajectories of adjustment disorder symptoms in post-treatment breast cancer survivors

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Abstract

Objective: Breast cancer survivors (BCS) may experience problems to adjust to their situation after cancer treatment completion. In case of severe distress, an adjustment disorder (AD) might develop. This study investigates the course of AD symptoms during one year and its predictors in BCS up to five years post-treatment.

Methods: BCS completed the Hospital Anxiety and Depression Scale (HADS) at baseline, three, six and twelve months. HADS-total scores were defined as no mental disorder (MD) symptoms (≤10), AD symptoms (11-14), and any other MD symptoms (≥15). Over the course of four assessments, symptom trajectories were a-priori defined as no MD symptoms, AD symptoms, fluctuating AD symptoms below and above cut-offs, or any other MD symptoms. Complementary, latent class growth analysis (LCGA) was used to identify data-driven trajectories.

Results: Among 293 BCS with complete data, the majority was classified as no MD symptoms (54.4%), followed by 37.5% in the fluctuating AD symptoms trajectory. Only 1.4% had AD symptoms and 6.8% had any other MD symptoms. With LCGA (N=459) three trajectories were found: stable no MD symptoms (58.6%), stable AD symptoms (32.9%) and high increasing any other MD symptoms (8.5%). Compared to BCS with no MD symptoms, BCS with fluctuating AD symptoms or any other MD symptoms were younger, less able to handle daily activities, and showed more social support discrepancy, neuroticism and less optimism.

Conclusions: Results of our study showed that AD symptoms in BCS up to five years post-treatment fluctuate over one year. It is thus important to appropriately assess AD over the course of five years post-treatment as AD symptoms can fluctuate.

Background

Breast cancer is the most prevalent cancer type in women. Improved methods for early cancer detection and innovations in cancer treatment has increased the 5-year survival rate in breast cancer survivors (BCS), which is currently 91% in the Netherlands (American Cancer Society, 2020; Nederlandse Kankerregistratie (NKR), 2020). As a consequence, more BCS are dealing with the long-term complications of their cancer treatment, including the psychological burden (Armes et al., 2009; Costanzo et al., 2007; Kostev et al., 2017; Stanton, 2012). When cancer-related distress is severe, an adjustment disorder (AD) can be diagnosed (Casey, 2009; Stevens & Rodin, 2011), if symptoms are not solely an exacerbation of a pre-existing mental disorder (MD) and the criteria of another MD are not met. In the Netherlands, reimbursement of psychological interventions for cancer survivors is available if a MD such as an anxiety disorder or major depression is diagnosed. It is currently being investigated whether AD can be added to the reimbursement scheme.

In the DSM-5, AD has been defined as the presence of emotional and behavioural symptoms in response to an identifiable stressor(s) occurring within three months of the onset of the stressor(s). The accompanied distress is out of proportion to normal reactions to the stressor in social or cultural context. After ceasing of the stressor or its consequences, symptoms of AD resolve within six months (Criterion E); however, if stressors or its consequences continue, this may result in persistent AD (American Psychiatric Association, 2013). After curative cancer treatment, continuous confrontation with stressors is possible due to for instance ongoing adjuvant endocrine therapies, imaging, and follow-up appointments as well as long-term consequences of cancer such as fatigue, fear of cancer recurrence, and reduced ability to work. Critics debate that a MD diagnosis based on distress symptoms alone medicalizes problems of living (Bachem & Casey, 2018) and that the AD diagnosis is unclear in discriminating a MD from a normal stress reaction (Casey, 2009). More insight in AD in relation to trajectories of psychological adjustment after cancer is necessary.

Predictors of AD related to cancer have not been thoroughly investigated (Carta et al., 2009). In a large mixed cancer sample (N=2141) higher education, having metastases and being female were identified as predictors for AD (Hund et al., 2016). In another study in cancer patients, the more commonly investigated symptom distress was found to be predicted by more neuroticism and findings on optimism were inconclusive(Cook et al., 2018).

Among patients with breast cancer, the prevalence of AD was estimated to be 7.1% in the acute phase of treatment (Mehnert & Koch, 2007), 38.6% in the first year post-diagnosis (Tang et al., 2020), 14.4% in BCS (Mehnert et al., 2014) and 20% in BCS with a first recurrence of breast cancer (Kissane et al., 2004) when assessed with (semi)structured interviews, the golden standard to diagnose AD in clinical settings (Mitchell et al., 2011). It is advised to screen patients with cancer for psychosocial problems prior to conducting clinical assessments (Riba et al., 2019). Although screening is common for depression (Beck et al., 1996), anxiety (Ibbotson et al., 1994) and posttraumatic stress disorder (Andrykowski et al., 1998), measures focussing on AD, e.g. Adjustment Disorder New Module (Maercker et al., 2007), the Diagnostic Interview Adjustment Disorder (Cornelius et al., 2014) and International Adjustment Disorder Questionnaire (Shevlin et al., 2020) are mostly used for research purposes. The Hospital Anxiety and Depression Scale (HADS), a commonly used screening questionnaire in cancer survivors, measures emotional distress with symptoms of depression and/or anxiety (Vodermaier & Millman, 2011). Since these symptoms are in line with the diagnostic criteria of AD, the HADS might also be used to screen for AD symptoms. Several studies have reported that the HADS is sensitive to identifying cases of AD in patients with cancer (Akizuki et al., 2003; Kugaya et al., 1998; Ozalp et al., 2008).

Understanding the course of AD symptoms over time may help identify BCS who develop persistent AD. Distinct distress trajectories in patients with breast cancer were observed up to 8 months post-diagnosis (Henselmans et al., 2010; Kant et al., 2018; Lam et al., 2010; Lotfi-Jam et al., 2019). Only one study followed BCS up to 4 years (Helgeson et al., 2004). Distress trajectories were identified as stable low (36%-80%), stable high (9%-15.4%) (Helgeson et al., 2004; Henselmans et al., 2010; Kant et al., 2018; Lam et al., 2010; Lotfi-Jam et al., 2019), recovery (5.6% and 12%) (Lam et al., 2010; Lotfi-Jam et al., 2019), delayed recovery (7%-27%) (Helgeson et al., 2004; Kant et al., 2018; Lam et al., 2010) and worsening (4.5% and 7.9%) (Kant et al., 2018; Lotfi-Jam et al., 2019). One study identified distress trajectories during active treatment (33.3%) and during the re-entry and survivorship phase (15.2%) (Henselmans et al., 2010). Predictors that distinguished trajectories were age (Lam et al., 2010), physical symptoms (Lam et al., 2010; Lotfi-Jam et al., 2019) at treatment completion (Kant et al., 2018), satisfaction with medical consultation (Lam et al., 2010), history of psychiatric illness (Lotfi-Jam et al., 2019), personal (Helgeson et al., 2004) and social resources (Helgeson et al., 2004; Lotfi-Jam et al., 2019), mastery (Henselmans et al., 2010; Lotfi-Jam et al., 2019), optimism (Henselmans et al., 2010; Lam et al., 2010), neuroticism (Henselmans et al., 2010), and benefit finding (Lotfi-Jam et al., 2019). Most studies (Helgeson et al., 2004; Henselmans et al., 2010; Kant et

al., 2018; Lam et al., 2010) used a growth mixture modelling approach to determine trajectories from a data-driven point of view, one study used cut-off scores from a clinical point of view (Lotfi-Jam et al., 2019).

The primary aim of this study was to detect trajectories of AD symptoms during one year using the HADS in BCS, using both clinically relevant cut-off scores and a data-driven growth modelling approach. The secondary aim was to identify predictors for distinct trajectories.

Methods

Participants and Procedure

Physicians invited 1205 BCS from three hospitals in the Netherlands to participate with an information letter. Eligible participants were cancer-free, ≥18 years old, with stage I-III breast cancer treated with curative intent, who finished primary cancer treatment in the past 5 years and were able to complete questionnaires in Dutch. BCS currently on hormonal therapy or treatment with specific antibodies (trastuzumab) were also eligible. After informed consent, participants received a questionnaire booklet (paper-and-pencil) or email with a link to a secured online system. Questionnaires were sent upon enrolment and after 3, 6 and 12 months.

Demographic, clinical and psychosocial measures

Participants completed socio-demographic variables (e.g. age, and employment status) and self-reported clinical variables, (e.g. type of treatment and time since diagnosis) in the baseline questionnaire.

AD symptoms were assessed using the HADS, a 14-item questionnaire with subscales Anxiety (HADS-A, 7 items) and Depression (HADS-D, 7 items) (Spinhoven et al., 1997). Items are scored on a scale (range 0-3, resulting in subscale (0-21) and HADS-total (0-42) scores. For cancer survivors (Vodermaier & Millman, 2011) cut-off scores were identified of HADS-total ≥10 or 11 for screening for MDs (sensitivity .80; specificity .74) and ≥15 for screening for depression (sensitivity .87; specificity .88).

Social support was measured with the Social Support List-Discrepancies (SSL-D), a 34-item questionnaire (4-point Likert scale). The SSL-D measures the perceived discrepancy between the amount of received social support and the desired amount of social support (van Sonderen, 2012), further referred to as social support discrepancy. A higher total score of SSL-D (range 34-102) indicates more social

support discrepancy. The test-retest reliability is .85 and a Cronbach's alpha of .95 (van Sonderen, 2012).

Optimism was measured with the Life Orientation Test (LOT), a 12-item questionnaire (5-point Likert scale, 0="strongly disagree" to 4="strongly agree) reflecting generalised optimism versus pessimism. Higher total scores (range 0-32, 4 filler items excluded) indicated more optimism. LOT-total Cronbach's alpha is .76 and test-retest reliability is .79 (Scheier & Carver, 1985).

Neuroticism was measured using the Big Five Inventory (BFI) (Denissen et al., 2008), a 44-item questionnaire designed to measure the Big Five factor structure of personality (5-point Likert scale). The Neuroticism subscale (BFI-N) measures the trait of neuroticism opposed to emotional stability, with increasing scores indicating a larger tendency to experience negative emotions. This version of the BFI has a Cronbach's alpha of 0.86.

AD symptoms and trajectories

Our definition of 'AD symptoms' was theoretically derived from the DSM-5 definition of AD, which describes that AD symptoms are characterized by marked distress, while the distress should not meet criteria for another MD. Cut-off thresholds for the HADS have been established that are sensitive to detect any MD (score ≥ 11) and depression (score ≥ 15)(Vodermaier & Millman, 2011). As such, we have assumed that a HADS score of 11 to 14 (i.e., marked distress but not depression) are indicative of AD symptoms. This is in line with previous studies reporting that the optimal HADS total score for screening for AD is 10 or 11(Akizuki et al., 2003; Kugaya et al., 1998; Ozalp et al., 2008). Thus, we predefined categories on HADS-total: (1) ≤10 was defined as "no MD symptoms", (2) 11 to 14 as "AD symptoms", and (3) ≥15 as "any other MD symptoms". Trajectories were created based on HADS-total over four assessments and defined as (a) no MD symptoms at all four assessments, (b) AD symptoms at all four assessments, (c) any other MD symptoms at all four assessments, and (d) fluctuating AD symptoms, i.e. an increase, decrease or irregular pattern of HADS-total.

Data processing and statistical analyses

Missing item scores on the HADS were replaced by the participants' subscale mean if at least four subscale items were answered (Bell et al., 2016). Participants who completed the HADS all four assessments were considered completers, and participants who had a missing HADS or did not report date of birth or time since diagnosis, were considered non-completers. Completers and non-completers were compared on demographic and clinical variables using t-tests for continuous

variables and chi-square tests for categorical variables. Completers were assigned into our a-priori defined trajectories based on their score above or below cut-off scores, and trajectories were compared on demographic and psychosocial variables with univariate testing (one-way ANOVA, chi-square tests and post hoc analysis). Variables that were significantly associated with trajectories membership were entered in a final multinominal regression analysis. Analyses were performed with SPSS version 25.

Latent class growth analysis (LCGA) was conducted using MPlus version 7 to identify data-based trajectories (classes) over time for HADS-total, following the guidelines described by Jung and Wickrama (Jung & Wickrama, 2008). By estimates individual differences (variability) in parameters reflecting participants' change in outcome over time, individuals are classified into latent classes based upon similar patterns in the outcome of interest (HADS). MPlus' full information maximum likelihood estimation for handling missing data was applied.

Following the guidelines, a single-class growth curve model was specified, as well as a three-class model. To determine the number of classes, the three-class model was compared with a two-class and four-class model, and the four-class model was compared with a three-class and five-class model. In total, the fit of five unconditional latent class models (i.e., models with no covariates) were estimated, with one to five linear classes. The number of classes was determined based on fit indices, model parsimony, and clinical interpretability. The model with the best fit has the smallest Bayesian Information Criterion (BIC), and significant p-values ($p<0.05$) for the Vuong-Lo-Mendell Ruben Likelihood Ratio Test (LMR-LRT) and the Bootstrap Likelihood Ratio Test (BLRT), which indicate that a model with a k number of classes has a better fit than a model with k-1 number of classes. Other considerations were a higher entropy statistic (near 1.0), indicating the degree to which latent trajectories may be clearly distinguished, and higher posterior probabilities of group membership (near 1.0), indicating the degree to which individuals have been correctly classified into a class. For clinical interpretability, we also considered the number of participants (not less than 5% of total sample ($n\geq23$)) of the identified classes. For each individual patient in the database, the predicted class of the best fitting model (i.e., with the optimal number of subgroups) was obtained.

Results

Sample characteristics

Of the 1205 eligible BCS who were invited, 459 participants (38.1%) consented and completed the HADS at least once. Demographic and clinical variables of completers, non-completers and the full sample are shown in Table 1. Compared to non-completers, completers were older (p=0.002) and had a lower education level (p=0.026).

Table 1. Socio-demographic and medical characteristics of participants

		Completers N=293 (Valid %)	Non-completers N=166 (Valid %)	Full study sample N=459 (Valid %)
Dutch nationality		287 (98.0%)	162 (98.8%)	449 (99.3%)
Age (mean, years (SD[a]; range))		57.8 (9.3; 33.0-87.6)	54.8 (10.0; 33.2-83.8)	56.7 (9.7; 33.0-87.6)
Marital status		228 (78.4%)	138 (83.6%)	366 (80.3%)
Children		240 (82.5%)	143 (86.7%)	383 (84.0%)
Education	Primary	65 (22.6%)	24 (14.7%)	89 (16.0%)
	Secondary	146 (50.7%)	78 (47.9%)	224 (49.7%)
	Tertiary	77 (26.7%)	61 (37.4%)	138 (30.6%)
Time since diagnosis (mean, months)		33.1 (SD 16.1)	33.1 (SD 16.1)	33.3 (SD 16.0)
Time since end of treatment (mean, months)		26.8 (SD 16.6)	28.7 (SD 16.8)	28.6 (SD 16.7)
Breast saving surgery		189 (64.5%)	98 (60.1%)	287 (62.9%)
Ablatio		39 (13.3%)	19 (11.7%)	58 (12.7%)
Breast amputation		75 (25.6%)	55 (33.7%)	130 (28.5%)
Chemotherapy		206 (70.3%)	123 (75.0%)	329 (72.0%)
Radiotherapy		226 (77.4%)	121 (73.8%)	347 (76.1%)
Hormone therapy		193 (65.9%)	102 (62.2%)	295 (64.6%)
Trastuzumab/Herceptin		37 (12.7%)	24 (14.6%)	61 (13.4%)

[a]: Standard Deviation

Trajectories based on cut-off scores

At group level, the average of all four HADS-assessments was 72.1% with no MD symptoms, 12.9% AD symptoms, and 15.0% any other MD symptoms. Classification in trajectories resulted in 157 BCS (53.6%) in the trajectory no MD symptoms, 4 BCS (1.4%) in the trajectory AD symptoms, 20 BCS (6.8%) in the trajectory any other MD symptoms, and 112 BCS (38.2%) in the trajectory fluctuating AD symptoms.

Predictors of trajectories based on cut-off scores

Given the low number of BCS in the trajectory AD symptoms, these BCS were merged with the trajectory fluctuating AD symptoms (stable&fluc-AD symptoms) and compared to the trajectory no MD symptoms and trajectory any other MD symptoms on demographic and psychosocial characteristics at baseline (Table 2).

In univariate analyses, a difference between trajectories was observed for age ($p=.041$), previous psychological counselling ($p\leq0.001$), perceived social support discrepancy ($p\leq0.001$), optimism ($p\leq0.001$), neuroticism ($p\leq0.001$), experience of a recent life event ($p<0.040$) and being able to handle daily activities ($p=.037$).

The seven significant predictors were entered simultaneously in the multinominal logistic regression analysis with the trajectory no MD symptoms as the reference group (Table 2). The final model was statistically significant ($X^2 = 166.9$, $df = 14$, $p\leq.001$, Cox & Snell $R^2 = 0.45$, Nagelkerke $=0.54$, McFadden $=0.34$). Experiencing a recent life event and previous psychological counselling did not contribute significantly to the overall statistical model (Table 2). Compared to BCS in the reference group, BCS in the trajectories stable&fluc-AD symptoms and any other MD symptoms were less able to handle daily activities, perceived a larger social support discrepancy, and showed less optimism and more neuroticism. Additionally, BCS in the trajectory stable&fluc-AD symptoms were younger compared to BCS in the reference group.

Table 2. Trajectories based on cut-off scores: Characteristics & multinominal regression analysis (Stable&fluc-AD[a] and Indication other MD[b] versus No MD indication[c])

	No MD indication			Stable&fluc-AD				Indication other MD			
Predictor		**X²**	**p**		**B**	**Wald**	**Exp (B (95% CI)**		**B**	**Wald**	**Exp (B) (95% CI)**
Intercept	n.a	7.2	**.028**	n.a	-3.17	2.05	n.a.	n.a	-10.75	**6.56****	n.a.
Age (mean years (SD[d]; range))	58.9 (8.5; 37-87)	7.4	**.025**	56.1 (9.7, 33-78)	-0.34	**4.07***	0.96 (0.93 - 1.00)	58.5 (11.4, 32-82)	0.02	0.47	1.02 (0.96 - 1.09)
Education Primary	34 (21.8%)	n.a	n.a	23 (20.3%)	n.a	n.a	n.a	8 (40%)	n.a	n.a	n.a
Education Secondary	82 (54.1%)			54 (47.8%)				10 (50%)			
Education Tertiary	39 (25.1%)			36 (31.9%)				2 (10%)			
Marital status (yes/no)	123/33	n.a.	n.a	26/89	n.a.	n.a.	n.a.	4/16	n.a.	n.a.	n.a.
Time since diagnosis (mean months (SD))	33.9 (15.9)	n.a.	n.a.	32.3 (16.3)	n.a.	n.a.	n.a.	31.1 (16.7)	n.a.	n.a.	n.a.
Medical treatment satisfaction (0-4 (SD))	3.5 (0.7)	n.a.	n.a.	3.3 (0.6)	n.a.	n.a.	n.a.	3.1 (1.0)	n.a.	n.a.	n.a.
Ability to handle daily activities well (1-5 (SD))	1.6 (0.7)	7.2	**.027**	2.1 (0.8)	0.55	**5.55***	1.74 (1.10 - 2.76	2.5 (0.9)	0.56	**5.64***	1.75 (1.10 - 2.78)
Recent life event (yes/no)	109/48	3.9	.140	62/52	0.53	2.55	1.70 (0.89 - 3.28)	13/7	-0.28	0.17	0.76 (0.20 - 2.86)
Previous psychological counselling (yes/no)	121/34	3.3	.189	64/52	0.21	0.32	1.23 (0.60 - 2.54)	6/14	1.31	3.12	3.72 (0.87 - 15.97)
Social support (SD)	39.1 (7.4)	19.3	**<.001**	46.5 (12.1)	0.06	**15.67*****	1.07 (1.03 - 1.10)	56.5 (18.4)	0.09	**14.73*****	1.10 (1.05 - 1.15)
Optimism (SD)	27.4 (4.2)	8.0	**.018**	23.7 (4.1)	-0.10	**4.41***	0.91 (0.83 - 0.99)	19.5 (5.1)	-0.22	**6.40***	0.81 (0.68 - 0.95)
Neuroticism (SD)	18.6 (4.7)	22.4	**<.001**	24.2 (4.6)	0.16	**15.91*****	1.18 (1.09 - 1.28)	28.2 (4.6)	0.28	**12.14*****	1.32 (1.13 - 1.55)

*p≤.05, **p≤.01, ***p≤.001

[a]: stable and fluctuating symptoms indicative for AD; [b]: symptoms indicative for other MD; [c]: indication for no MD; [d]: standard deviation

Trajectories based on LCGA

Using LCGA for the complete sample (N=459), the intercept of the HADS-total was 7.6 (95% confidence interval [CI] 7.0-8.1, p≤0.001), which can be interpreted as no MD symptoms at baseline. There was a non-significant slope (0.04; 95% CI -0.11 to 0.19, p=0.630), which can be interpreted as a stable HADS-total during one year. The most appropriate choice based on fit indices, internal reliability, and interpretability was a three-class model (Table 3). The first trajectory consisted of 269 BCS (58.6%) and was defined as 'stable no MD symptoms' (low), as participants reported low baseline HADS-total scores (intercept 3.60; 95% CI 3.09-4.11) with a non-significant slope (-0.09 (95% CI -0.26-0.07)). The second trajectory was defined as 'stable AD symptoms' (AD symptoms). For this trajectory of 151 BCS (32.9%), the intercept was 11.38 (95% CI 10.23-12.54) with a non-significant slope (-0.1; 95% CI -0.39-0.19). The third trajectory was defined as 'high increasing any other MD symptoms' (high increasing). For this trajectory of 39 BCS (8.5%), the intercept was 19.83 (95% CI 17.54-22.12) with a significantly increasing slope (1.29; 95% CI 0.30-2.29).

Predictors of trajectories based on LCGA

Univariate analyses (Table 4) showed differences between trajectories for age (p=0.015), satisfaction with medical treatment (p<0.004), being able to handle daily activities (p<0.003), previous psychological counselling (p≤0.001), experiencing a recent life event (p=0.010), social support discrepancy (p≤0.001), optimism (p≤0.001) and neuroticism (p≤0.001).

These eight predictors were included in the final model with the low trajectory as reference group. The final model was statistically significant (χ^2 = 264.5, *df* = 16, p≤0.001, Cox & Snell R^2 = 0.46, Nagelkerke = 0.55, McFadden = 0.35). Age, ability to handle daily activities, social support discrepancy, neuroticism and optimism contributed significantly to the statistical model. BCS in the AD symptoms trajectory and the high increasing trajectory were less able to handle daily activities, perceived a larger social support discrepancy, and showed more neuroticism compared to BCS in the low trajectory. BCS in the AD symptoms trajectory were younger compared to BCS in the low trajectory, and BCS in the high increasing trajectory reported less optimism compared to BCS in the low trajectory.

Table 3. Fit indices, entropy and average posterior probabilities across models with different number of classes by HADS[a]-score

No. of classes	BIC[b]	LMR-LRT[c]	BLR-T[d]	Entropy	n	Posterior probabilities	Intercept (95%CI[e])	Slope linear (95%CI)
2	9684.567	0.0048	0.0000	0.885	350 (76.3%)	0.968	**4.79 (4.02 - 5.56)*** **	-0.06 (-0.22 - 0.09)
					109 (23.7%)	0.953	**15.68 (13.81 - 17.55)*** **	0.29 (-0.25 - 0.82)
3	9328.060	0.0001	0.0000	0.880	269 (58.6%)	0.960	**3.60 (3.09 - 4.11)*** **	-0.09 (-0.26 - 0.07)
					151 (32.9%)	0.918	**11.38 (10.23 - 12.54)*** **	-0.10 (-0.39 - 0.19)
					39 (8.5%)	0.938	**19.83 (17.54 - 22.12)*** **	**1.29 (0.30 - 2.29)***
4	9212.377	0.0200	0.0000	0.823	201 (43.8%)	0.916	**2.59 (2 - 3.18)*** **	-0.07 (-0.22 - 0.08)
					75 (16.3%)	0.903	**14.04 (12.74 - 15.33)*** **	-0.14 (-0.7 - 0.42)
					32 (7.0%)	0.951	**20.50 (18.12 - 22.88)*** **	**1.48 (0.36 - 2.6)****
					151 (33.0%)	0.847	**7.90 (6.7 - 9.1)*** **	-0.03 (-0.37 - 0.31)
5	9201.561	0.3348	0.0000	0.761	158 (34.4%)	0.892	**2.09 (1.66 - 2.51)*** **	-0.07 (-0.21 - 0.07)
					48 (10.4%)	0.864	**15.35 (13.69 - 17.01)*** **	-0.26 (-0.87 - 0.35)
					31 (6.71%)	0.942	**20.52 (18.04 - 23.01)*** **	**1.53 (0.36 - 2.7)*****
					133 (29.0%)	0.774	**6.13 (5.09 - 7.17)*** **	-0.02 (-0.4 - 0.35)
					89 (19.4%)	0.784	**10.45 (8.23 - 12.68)*** **	-0.05 (-0.61 - 0.51)

*p≤.05, **p≤.01, ***p≤.001

[a]: Hospital Anxiety and Depression Scale; [b]: Bayesian Information Criterion; [c]: Vuong-Lo-Mendell Rubin Likelihood Ratio Test; [d]: Bootstrap Likelihood Ratio Test; [e]: confidence interval;

Table 4. Trajectories based on LCGA[a]: Characteristics & multinominal regression analysis (AD trajectory[b] and High increasing trajectory[c] versus Low trajectory[d])

		Low trajectory			AD trajectory				High increasing trajectory			
Predictor			**X^2**	**p**		**B**	**Wald**	**Exp (B) (95% CI)**		**B**	**Wald**	**Exp (B) (95% CI)**
Intercept		n.a.	8.4	**0.015**	n.a.	-3,36	3.13	n.a.	n.a.	-8.87	**7.78****	n.a.
Age (mean years (SD[e]; range)		57.8 (9.4; 33-87)	8.3	**0.016**	55.1 (9.6; 33 - 78)	-0.04	**7.96*****	0.96 (0.93 - 0.99)	55.5 (10.9; 32 - 82)	-0.03	1.67	0.97 (0.92 - 1.02)
Education	Primary	46			31				12			
	Secondary	136	n.a.	n.a.	69	n.a.	n.a.	n.a.	19	n.a.	n.a.	n.a.
	Tertiary	84			47				7			
Marital status (yes/no)		214 / 54	n.a.	n.a.	119 / 30	n.a.	n.a.	n.a.	33 / 6	n.a.	n.a.	n.a.
Time since diagnosis (mean months (SD))		34.0 (15.7)	n.a.	n.a.	32.8 (16.2)	n.a.	n.a.	n.a.	30.8 (16.8)	n.a.	n.a.	n.a.
Medical treatment satisfaction (0-4 (SD))		3.5 (4.7)	5.0	0.08	3.2 (0.6)	-0.43	**4.24***	0.65 (0.43 - 0.98)	3.1 (0.9)	-0.06	0.03	0.94 (0.46 -1.93)
Ability to handle daily activities well (1-5 (SD))		1.6 (0.7)	18.8	**<.001**	2.1 (0.7)	0.63	**10.53*****	1.87 (1.28 - 2.73)	2.5 (0.9)	1.24	**15.99*****	3.46 (1.88 - 6.37)
Previous life event (yes/no)		87 / 180	1.9	0.382	70 / 78	0.31	1.26	1.36 (0.79 - 2.35)	17 / 22	-0.12	0.06	0.89 (0.34 - 2.35)
Previous psychological counselling (yes/no)		69 / 198	0.9	0.642	74 / 77	0.25	0.72	1.29 (0.72 - 2.31)	24 / 15	0.00	0.00	1.00 (0.36 - 2.82)
Social support (SD)		39.7 (8.5)	24.6	**<.001**	46.8 (12.1)	0.06	**16.91*****	1.06 (1.03 - 1.08)	54.8 (16.3)	0.08	**18.91*****	1.09 (1.05 - 1.13)
Optimism (SD)		27.4 (4.2)	13.1	**0.001**	23.9 (4.1)	-0.07	3.27	0.93 (0.87 - 1.01)	20.1 (4.6)	-0.22	**11.99*****	0.81 (0.71 - 0.91)
Neuroticism (SD)		18.6 (4.6)	56.7	**<.001**	24.3 (4.5)	0.21	**35.89*****	1.24 (1.15 - 1.32)	28.3 (4.9)	0.34	**32.23*****	1.40 (1.25 -1.57)

*p≤.05, **p≤.01, ***p≤.001

[a]: latent class growth analysis; [b]: symptoms indicative for AD; [c]: high increasing symptoms indicative for any other MD; [d]: indication for no MD; [e]: standard deviation

Discussion

In this study, three distinct one-year trajectories in HADS-scores were found in BCS using two different statistical approaches: one approach with clinical cut-off scores to indicate AD symptoms or MD symptoms and one data-driven approach to predict classes of BCS with a similar course of AD symptoms or MD symptoms. The 'low' trajectory was found in more than half of the BCS. The second trajectory with (fluctuating) AD symptoms was found in about one third of the BCS. The trajectory with (high increasing) any other MD symptoms was found in fewer than one in ten BCS. Furthermore, the approach based on cut-off scores showed a very low (1.4%) percentage of BCS with stable AD symptoms, and fluctuating scores below and above cut-off scores in almost 40% of the participants. With the latent modelling approach, we found a trajectory AD symptoms in one-third of the BCS, with a wide confidence interval of HADS-scores per assessment and no significant change over time. Thus, both statistical approaches showed that AD symptoms can fluctuate in a significant proportion of BCS over time and that a pattern of stable AD symptoms was not present in this sample. This questions the validity of the diagnosis AD in BCS.

The detection of the low trajectories and (high increasing) any other MD symptoms is in line with previous trajectory studies (Helgeson et al., 2004; Henselmans et al., 2010; Kant et al., 2018; Lam et al., 2010; Lotfi-Jam et al., 2019). These studies all reported trajectories as 'resilient' and 'chronic', with a stable course of few and high symptoms post-treatment up to 6 months (Henselmans et al., 2010; Kant et al., 2018; Lotfi-Jam et al., 2019), 8 months (Lam et al., 2010) and 4 years (Helgeson et al., 2004). Non-stable trajectories were observed in all previous studies as well. Our study provided additional detailed observations by means of multiple assessments within a one-year period, indicating more individual fluctuations in AD symptoms than was expected based on earlier findings. Fluctuations in AD symptoms were found independent of time since diagnosis, which is not in line with the DSM-5 definition of AD (American Psychiatric Association, 2013) which assumes that AD diminishes over time, implying a self-healing process (Casey & Bailey, 2011). The discrepancies between this study and the established AD criteria stress the debate of AD diminishing after six months after AD symptom occurrence or becoming persistent in case of ongoing stressors in the cancer survivor context. Therefore, future research could be directed towards exploring acute and persistent AD immediately post-diagnosis, and whether symptoms might fluctuate over time.

Compared to BCS in the trajectories with no MD symptoms, characteristics of BCS in the trajectories of AD symptoms or MD symptoms were a larger social support discrepancy,

less optimism and more neuroticism. These findings are in line with previous trajectory studies, where less social support (Helgeson et al., 2004; Lotfi-Jam et al., 2019), less optimism (Henselmans et al., 2010; Lam et al., 2010) and higher scores on neuroticism (Henselmans et al., 2010; Lam et al., 2010) were observed in 'chronic distress' or 'lower mental functioning' trajectories. Lower ability to handle daily activities is in line to the criteria of AD (American Psychiatric Association, 2013), where poorer functioning in social relations, work or study is observed in people who are diagnosed with AD. Lastly, with the exception of Lam et al. (Lam et al., 2010), previous trajectory studies did not find age differences between trajectories, which is contradictory to our study. BCS with a trajectory of (fluctuating) AD symptoms were almost three years younger compared to BCS belonging to the trajectory no MD symptoms. A systematic review including cross-sectional and longitudinal studies found that a younger age increased the risk of distress (Syrowatka et al., 2017). These previous findings regarding predictors combined with the results of our study emphasize the relevance for clinicians to monitor these predictors to detect vulnerable BCS showing AD symptoms.

Study limitations

The results should be interpreted carefully because of selection bias in the study sample. Participants who completed all questionnaires were older and lower educated compared to participants who did not complete all questionnaires, although the sample used for the cut-off score analysis was comparable to the sample in the LCGA analysis. Furthermore, analysis of the predictive value of education was not possible due to too small cells, resulting in inconclusive findings on education. In our study, we assessed whether participants had previously received psychological counselling. We did not, however, assess whether participants had a history of mental illness, which could have been an important predictor to developing AD. This study was an additional analysis of a dataset on the course of fear of cancer recurrence (FCR) over time in BCS (Custers et al., 2020). Secondary analyses reduce research participation burden, but results might be less generalisable to the overall BCS population, since BCS signed up for research investigating FCR instead of AD related to cancer.

For research purposes, the analyses of the HADS are of great value to gain insight in which BCS are at risk for AD. The HADS, however, does not assess impairments in social or occupational functioning, which is a limitation. While not assessed thoroughly in our study, BCS with a trajectory of (fluctuating) AD symptoms reported less ability to handle daily activities and had a larger perceived social support discrepancy. A diagnostic interview, use of an AD-specific questionnaire or combining measures would capture AD more accurately. Finally, due to the small number of participants with AD symptoms, we were not able to further categorize subtypes of AD.

Clinical implications

This study used two different approaches to analyse the data, combining methodologies used in previous studies to observe the course of AD symptoms: a clinical point of view in using a cut-off score to screen for a possible AD or MD, and a statistical point of view to predict latent classes based on scores over time. Both methodologies detected fluctuating symptoms over time. This would imply that conclusions based on single assessment HADS-scores in clinical practice would not be sensitive enough to detect those patients with AD symptoms, and for whom a diagnosis of AD might be applicable.

Conclusion

A substantial proportion of BCS up to 5 years post-diagnosis showed fluctuating AD symptoms and only a negligible percentage of the cases had a stable course of AD symptoms. We suggest handling single assessment cut-off scores with caution.

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Chapter 3

Evaluating time-limited and persistent symptoms of adjustment disorder in cancer patients following a colorectal cancer diagnosis: a longitudinal observational study

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Abstract

Background: Colorectal cancer (CRC) patients may experience symptoms of adjustment disorder (AD) after cancer diagnosis and treatment. Time-limited symptoms of AD may become persistent if the stressor or its consequences have not disappeared after six months, but evidence on the course of AD symptoms is scarce. This longitudinal observational study investigates the proportion of CRC patients with time-limited and persistent AD symptoms within the first year after diagnosis, in relation to demographic, clinical and psychological factors and health-related quality of life (HRQoL).

Methods: Informed consent was retrieved from 232 participants and 194 participants completed questionnaires at baseline, three, six- and twelve-months post-diagnosis. Hospital Anxiety and Depression Scale total scores (HADS-T) were categorized as indication for no symptoms of a mental disorder (MD) (HADS-T≤10), AD symptoms (HADS-T 11-14) and other MD symptoms (HADS-T≥15). Symptom subgroups over time were a priori defined: no MD, time-limited AD, persistent AD, other MD and fluctuating symptoms.

Results: Complete data were available for 81 participants (41.4%). Over time, 38.3% had no MD symptoms, 8.6% time-limited AD symptoms, 1.2% persistent AD symptoms, 4.9% other MD symptoms and 46.9% fluctuating symptoms. Participants with AD and fluctuating symptoms reported higher fear of cancer recurrence, lower HRQoL, and higher cancer-specific distress than participants without MD symptoms ($p<.05$).

Conclusions: During the first year after CRC diagnosis, only a small proportion of the patients showed time-limited and persistent AD symptoms, the majority showed fluctuating symptoms. More prospective research is needed to determine how repeated assessments for elevated AD symptoms relate to an AD diagnosis established with a diagnostic interview.

Background

An increasing number of people diagnosed with colorectal cancer (CRC) undergo cancer treatment with curative intent, and the 5-year survival rate is estimated at 66% in the Netherlands (Netherlands Cancer Registry (NCR) Netherlands Comprehensive Cancer Organisation (NCR, 2023). This results in more patients dealing with the consequences of cancer and/or its treatment. Research has expanded on psychosocial functioning among CRC survivors (CRCS) leading to a better understanding of the psychosocial challenges that CRCS face, especially following the transition from 'patient' to 'survivor' (Denlinger & Barsevick, 2009; Garofalo et al., 2009). A systematic review by Han et al. (Han, Yang, & Syrjala, 2020) found multiple adverse symptoms in CRCS after cancer treatment, such as cancer-related distress, symptoms of depression or anxiety, fear of cancer recurrence (FCR), negative body image and sexual problems.

In the case of significant emotional or behavioural symptoms, as evidenced by severe distress or impaired personal, occupational, and/or social functioning, an adjustment disorder (AD) may be present (American Psychiatric Association, 2013). Examples of AD symptoms include anxiety, depressed mood or feeling unable to cope with the stressful event (Stevens & Rodin, 2011). According to the DSM-V definition of AD, these symptoms develop 'in response to an identifiable stressor(s), occurring within three months of the onset of the stressor(s)… and once the stressor or its consequences are terminated, the symptoms do not persist for more than an additional six months' (American Psychiatric Association, 2013), suggesting AD being a time-limited condition (Stein et al., 2018). However, if the stressor or its consequences have not disappeared after six months, AD symptoms may continue in a persistent form(American Psychiatric Association, 2013). AD can be specified into six subtypes: depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of behavior, mixed disturbance of emotions and behavior, and unspecified (American Psychiatric Association, 2013). Stressors in CRC patients undergoing surgery may be present preoperatively (e.g., a negative emotional reaction to the diagnosis of cancer), postoperatively (e.g., a negative emotional reaction to surgery, mismatch of expectations and experience of recovery, dealing with distressing physical symptoms and complications after surgery), and across the continuum of the cancer experience (e.g., disruption of life) (Abelson et al., 2018). Having a stoma is specifically found to be negatively associated with physical and mental quality of life (Jansen et al., 2010).

Research on the prevalence of AD after CRC diagnosis is limited. In a mixed cancer type population, an AD prevalence rate of 6-19% was found when AD was assessed

with clinical interviews (Blazquez & Cruzado, 2016; Hund et al., 2016; Mitchell et al., 2011; Van Beek et al., 2022). One study among CRC in- and outpatients reported a four-week AD prevalence estimate of 10% based on the DSM-IV and the Composite International Diagnostic Interview for mental disorders adapted for cancer patients (Mehnert et al., 2014). Another study among elderly CRCS reported a prevalence rate of 0.04%-0.1% for AD with depressed mood measured over four years using the Surveillance Epidemiology and End-Results-Medicare data system applying the International Classification of Diseases-9 (Zhang & Cooper, 2010).

A clinical diagnostic interview is the gold standard to diagnose AD (Mitchell et al., 2011). Three instruments have been developed over the last few years that specifically target AD. The Diagnostic Interview for Adjustment Disorder (DIAD) (Cornelius et al., 2014) has been used to diagnose AD. The Adjustment Disorder New Module (ADNM) (Maercker et al., 2007) and International Adjustment Disorder Questionnaire (IADQ) (Shevlin et al., 2020) have been used to screen for AD symptoms. Although these instruments are upcoming in the clinical context of psychiatry (Maercker & Lorenz, 2018; O'Donnell et al., 2019), so far they have not been used in psychosocial research on cancer patients. In studying AD in cancer survivors over a longer period, these clinical interviews may be quite time consuming for clinicians and burdening for patients with the risk of high attrition rates in longitudinal study samples. Screening questionnaires can be helpful for a first evaluation of time-limited and persistent AD symptoms in cancer survivors. A questionnaire commonly used in psycho-oncology studies is the Hospital Anxiety and Depression Scale (HADS)(Zigmond & Snaith, 1983), which has been validated to screen for emotional distress in patients with cancer (Vodermaier & Millman, 2011), including CRC (Patel et al., 2011). The HADS has the potential to detect AD symptomatology, since it measures emotional symptoms which are important components of the AD classification. Previous studies have used the HADS in cancer patients to identify cases of AD (Akizuki et al., 2003; Kugaya et al., 1998; Ozalp et al., 2008). In the present study, the HADS will be used as an indicator to investigate AD symptoms over time.

The differentiation between time-limited and persistent AD symptoms has gained little attention in cancer research. One study by Blazquez et al. investigated AD prevalence longitudinally in a mixed cancer group using the Mini-International Neuropsychiatry Interview combined with the DSM-IV criteria for AD (Blazquez & Cruzado, 2016). At the group level, 10.7% was diagnosed with AD before radiotherapy, 5.8% one week after finishing treatment, and 7.8% at one-month follow-up. How often time-limited or persistent (symptoms of) AD occurs following a cancer diagnosis has not been reported.

The primary objective of this study was to determine the proportion of patients with time-limited and persistent AD symptoms longitudinally within the first year after CRC diagnosis. The secondary objective was to identify demographic, clinical and psychological variables and health-related quality of life (HRQoL) associated with these AD symptoms.

Methods

Participants and Procedure

Participants were recruited from departments of surgery at eight Dutch medical centers between January 2012 and May 2013. Men and women were eligible to participate if they were newly diagnosed with CRC, were awaiting treatment with curative intent (surgery and/or neo-adjuvant chemotherapy) and were older than 18 years of age. Exclusion criteria were stage IV disease and Lynch syndrome. Participants had to be able to read and write in Dutch. Approval from the local Medical Ethics Committee was obtained prior to the start of the study (Commissie Mensgebonden Onderzoek regio Arnhem–Nijmegen, registration number 2011/404).

Prior to surgery, eligible patients received an information letter and the purpose of the study was explained by a research nurse. Patients who agreed to be contacted by the researcher (JC), received further information via telephone. After obtaining written informed consent, the participants received a questionnaire set that was sent out immediately after diagnosis (baseline), and at 3-, 6- and 12-months post-diagnosis. Participants who were unable to complete the first assessment due to the timing of their surgery were enrolled in the study at 3 months post-diagnosis. The research nurse at each hospital extracted medical data from the participants' medical records.

Demographic, clinical and psychological measures

Questionnaires were completed in a paper and pencil format. Participants completed items related to demographic (age, sex, education, marital status, children), clinical (tumor location (colon/rectum), adjuvant therapy (chemo- and/or radiotherapy), stoma), and psychosocial variables (psychological counselling by a psychologist/psychiatrist/social worker prior to CRC diagnosis, further referred to as previous psychological counselling, and the occurrence of previous life events).

AD symptoms were measured using the 14-item HADS (Spinhoven et al., 1997). Items are scored on a 4-point Likert scale (range 0-3). A total HADS score (HADS-T, range 0-42)

cutoff of 10 or 11 is sensitive to screen for any mental disorder (MD) (sensitivity 0.80; specificity 0.74), and ≥15 for depression (sensitivity 0.84; specificity 0.50) in cancer patients (Vodermaier & Millman, 2011). Since an AD diagnosis is applicable if criteria for another MD are not met (American Psychiatric Association, 2013), HADS-T between 11 and 14 were predefined as indicative for AD symptoms and HADS-T ≥15 for other MD symptoms. The HADS has a Depression (HADS-D, 7 items, range 0-21) and Anxiety (HADS-A, 7 items, range 0-21) subscale. The HADS-D and HADS-A were analyzed separately to observe possible differences in depression or anxiety symptoms in participants with time-limited and persistent AD symptoms. Both subscales had a cutoff score of ≥8 (HADS-D sensitivity 0.55, specificity 0.75; HADS-A sensitivity 0.67, specificity 0.67) for identifying cases (Singer et al., 2009). Cronbach's alpha of the baseline HADS-T in the current study was 0.90.

Social support was measured with the 34-item Dutch Social Support List-Discrepancies (SSL-D) (van Sonderen, 2012). The SSL-D measures the discrepancy between perceived social support and desired social support, further referred to as social support discrepancy, with items scored on a 4-point scale (1="Exactly the right amount"; 1="It happens too often"; 2="I don't really miss it, but I prefer more"; 3="I miss it"). The SSL-D total score ranges from 34 to 102, with a higher score indicating greater social support discrepancy. Cronbach's alpha for the current study is 0.87 at baseline.

Fear of cancer recurrence was measured using the Dutch version of the 6-item Cancer Worry Scale (CWS-6) (Custers et al., 2018) on a 4-point Likert scale (1="Never" to 4="Almost always"). The total score ranges from 6 to 24, with a higher score indicating a high level of FCR. Cronbach's alpha for the current study is 0.88 at baseline.

Health-related quality of life was measured using the 30-item European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, which evaluates health-related quality of life (HRQoL) in patients with cancer (Aaronson et al., 1993). The EORTC QLQ-C30 contains five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and a global quality of life scale. All scales were linearly transformed and range from a score of 0 to 100 for the overall total score, with a higher score reflecting better functioning or quality of life. Cronbach's alpha for the current study is 0.84 at baseline.

Cancer-specific distress was measured using the Dutch version of the 15-item Impact of Event Scale (IES) (Horowitz et al., 1979) which is scored on a 4-point scale (0=not at all; 1=rarely; 3=sometimes; 5=often). The total score ranges from 0 to 75, with a

higher score indicating greater adaptation difficulties after a traumatic experience. Cronbach's alpha for the current study is 0.91 at baseline.

Fatigue was measured using the 8-item fatigue severity subscale of the Checklist Individual Strength, Fatigue Severity Subscale (CIS-Fatigue) (Vercoulen et al., 1994) with a 7-point Likert scale (1=No, that is not true; 7=Yes, that is true). The total score ranges from 8 to 56, with a higher score indicating greater fatigue severity. Cronbach's alpha for the current study is 0.92 at baseline.

Subgroups of time-limited and persistent AD symptoms

To assess whether participants showed AD symptoms at a single assessment, categories were a priori defined: HADS-T <11 as no MD symptoms, HADS-T between 11 and 14 as AD symptoms and HADS-T ≥15 as other MD symptoms. To longitudinally assess the proportion of participants with time-limited and persistent AD symptoms, subgroups were defined a priori: (1) HADS-T <11 at all four assessments was defined as no MD symptoms, (2) HADS-T between 11 and 14 at baseline or at baseline and 3 months post-diagnosis was defined as time-limited AD symptoms, (3) HADS-T between 11 and 14 at baseline, 3 months and 6 months post-diagnosis or at all assessments was defined as persistent AD symptoms, (4) HADS-T ≥15 at all assessments was defined as other MD symptoms and (5) all other trajectories were defined as fluctuating AD and MD symptoms (further called fluctuating symptoms).

Data processing and statistical analyses

In case of missing HADS items, the item score was replaced with the participants' subscale mean if at least 50% of the items were answered. For each measurement, the number of participants per predefined category (no MD symptoms, AD symptoms, other MD symptoms) and the average HADS-T was calculated. Differences in demographic and clinical variables were compared between participants with four HADS measurements (completers) and three or fewer HADS measurements (non-completers) using t-tests and chi-square tests to detect possible response bias. Data from completers were included in the longitudinal analyses. Repeated measures ANOVA was conducted to detect possible time effects on the mean HADS-T at group level. The number of participants in each subgroup (no MD symptoms, time-limited AD symptoms, persistent AD symptoms, other MD symptoms, and fluctuating symptoms) was calculated. Paired sample t-tests were used to detect differences between subgroups on HADS-A and HADS-D at all measurement points. Subgroups were compared using ANOVAs, chi-square tests, and post hoc analyses on demographic, clinical, and psychological variables. All analyses were performed using SPSS version 25 using p-values of <.05 for indicating statistical significance.

Results

Sample characteristics

Informed consent was obtained from 232 participants and 194 participants completed at least one HADS measurement. The demographic and clinical characteristics of completers who completed all four measurements (N=81, 41.8%) and non-completers with one or more missing HADS measurements (N=113, 68.2%) are shown in Table 1. Reasons for not completing the questionnaire varied from being involved in active cancer treatment to being physically unable to participate in the study. Completers did not differ significantly from non-completers, except that more non-completers than completers had primary education and fewer completers than non-completers had secondary education (p=.047). At the group level, the mean HADS-T was 8.2 (SD=6.7) at baseline, 7.3 (SD=5.9) at 3 months, 8.0 (SD=6.0) at 6 months, and 8.3 (SD=6.7) at 12 months post-diagnosis.

Table 1. Demographic, medical and psychosocial characteristics of participants

		Completers[a] (N=81)	Non-completers (N=113)	p-value[c]	Full study sample (N=194)
Nationality, N (%)[b]	Dutch	79 (97.5)	113 (100.0)	n/a	192 (99.0)
Age in years, mean (SD)		67.1 (9.5)	67.5 (9.1)	.758	67.3 (9.2)
Gender, N (%)	Women	31 (38.3)	38 (33.6)	.505	69 (35.6)
	Men	50 (61.7)	75 (66.4)		125 (64.4)
Education, N (%)[b]	Primary	16 (20.0)	37 (35.2)	***.047***	53 (28.6)
	Secondary	42 (52.5)	39 (37.1)		81 (43.8)
	Tertiary	22 (27.5)	29 (27.6)		51 (27.6)
Living as married, N (%)[b]	Yes	72 (88.9)	16 (15.0)	.442	163 (86.7)
	No	9 (11.1)	91 (85.0)		25 (13.3)
One or more children, N (%)[b]	Yes	73 (90.1)	94 (87.0)	.513	167 (88.4)
	No	8 (9.9)	14 (13.0)		22 (11.6)
Tumour location, N (%)[b]	Colon	44 (63.8)	72 (70.6)	.349	116 (67.8)
	Rectum	25 (36.2)	30 (29.4)		55 (32.2)
Adjuvant therapy, N (%)[b]	Yes	39 (48.1)	31 (39.7)	.286	70 (44.0)
	No	42 (51.9)	47 (60.3)		89 (56.0)
Stoma, N (%)[b]	Yes	35 (43.2)	31 (43.7)	.955	66 (43.4)
	No	46 (56.8)	40 (56.3)		86 (56.6)
Social support discrepancy, N=144[b], mean (SD)[d]		38.5 (7.4)	40.6 (9.9)	.159	39.5 (8.6)

Table 1. Continued

	Completers[a] (N=81)	Non-completers (N=113)	p-value[c]	Full study sample (N=194)
Fear of cancer recurrence, N=132[b], mean (SD)[d]	13.4 (4.6)	13.6 (3.6)	.812	13.5 (4.5)
Quality of life, N=143[b], mean (SD)[d]	68.6 (18.2)	70.7 (20.3)	.516	69.5 (19.1)
Cancer-specific distress, N=133[b], mean (SD)[d]	17.5 (14.9)	15.1 (15.1)	.364	16.4 (15.0)
Fatigue, N=142[b], mean (SD)[d]	26.0 (13.0)	24.1 (12.9)	.396	25.2 (13.0)

Abbreviation: SD, standard deviation
[a]Completers filled in four HADS measurements, non-completers three or fewer HADS measurements
[b]Sample size due to missing values
[c]Independent sample t test for age and psychosocial variables, and chi-square test for gender, education, living as married, one or more children and clinical variables
[d]Values at baseline

Table 2 shows the mean HADS-T at all time points in the categories no MD symptoms, AD symptoms and other MD symptoms per assessment. Repeated measures analysis did not show a significant effect of time on HADS-T (F(3.43)=0.378, p=.769).

Table 2. Hospital Anxiety and Depression Scale (HADS) total scores of participants (N=194) over time

	Baseline	3 months	6 months	12 months
*No MD symptoms (HADS-total < 11)*mean (SD) N (%)[a]	3.9 (3.1) 104 (71.7%)	4.7 (3.2) 118 (76.6%)	4.8 (3.1) 98 (69.0%)	4.4 (3.3) 86 (67.2%)
AD symptoms (HADS-total 11-14) mean (SD) N (%)[a]	12.1 (1.0), 20 (13.8%)	12.7 (1.1) 21 (13.6%)	12.3 (1.2), 24 (16.9%)	11.9 (1.0) 15 (11.7%)
Other MD symptoms (HADS-total ≥ 15) mean (SD) N (%)[a]	20.8 (5.6) 21 (14.5%)	20.1 (3.4) 15 (9.7%)	18.9 (4.1) 20 (14.1%)	18.6 (3.8) 27 (21.1%)

Abbreviations: MD, mental disorder; SD, standard deviation; AD, adjustment disorder
[a]Due to missing values. Missing cases: baseline N=49, 3 months N=40, 6 months N=52, 12 months N=66

Subgroups of time-limited and persistent AD symptoms

In our study sample of 81 participants who completed all questionnaires, 31 participants showed no MD symptoms (38.3%), 7 showed time-limited AD symptoms (8.6%), 1 showed persistent AD symptoms (1.2%), and 38 showed fluctuating symptoms (46.9%). Four participants (4.9%) reported other MD symptoms. Given the low number of participants classified in the time-limited and persistent AD symptoms subgroups, all participants with time-limited AD symptoms, persistent AD symptoms, and fluctuating symptoms were merged into one group for follow-up analyses, defined as fluctuating symptoms (N=46). The other MD symptoms subgroup was not included in further analyses because of the low number of observations in this group (N=4).

Anxiety and Depression subscale scores

In the subgroup fluctuating symptoms (N=46), the mean HADS-A score was 5.2 (SD=3.0) at baseline, 4.1 (SD=2.9) at 3 months, 4.8 (SD=3.0) at 6 months, and 5.3 (SD=4.3) at 12 months post-diagnosis. The proportion of participants scoring above the cutoff was 17.1%, 11.7%, 18.2%, and 23.0% respectively. The mean HADS-A score was significantly lower at 3 months post-diagnosis compared to the other measurements (0.6-1.2 points, $p<.025$).

The mean HADS-D score was 4.5 (SD=3.1) at baseline, 5.1 (SD=3.3) at 3 months, 5.1 (SD=3.6) at 6 months, and 5.1 (SD=3.2) at 12 months post-diagnosis. The proportion of participants scoring above the cutoff was 12.4%, 14.3%, 13.4%, and 15.4% respectively. The mean HADS-D scores on the four measurements did not significantly differ from each other.

Characteristics of subgroups

There were no differences between the subgroups with no MD symptoms (N=31) and fluctuating symptoms (N=46) in demographic and clinical variables, or differences could not be analyzed due to the low number of participants in the cells (Table 3). The fluctuating subgroup had significantly higher FCR ($p=.003$), lower HRQoL ($p=.02$), and higher cancer-specific distress ($p=.001$) compared to the no MD symptoms subgroup.

Table 3. Characteristics of subgroups with no mental disorder (MD) symptoms and fluctuating symptoms

		No MD symptoms (N=31)	Fluctuating symptoms (N=46)	p-value[b]
Age in years, mean (SD)		69.0 (9.5)	65.9 (9.2)	0.163
Gender, N (%)	Women	10 (32.3)	18 (39.1)	0.539
	Men	21 (67.7)	28 (60.9)	
Education, N (%)[a]	Primary	8 (26.7)	6 (13.0)	n/a
	Secondary	18 (60.0)	23 (50.0)	
	Tertiary	4 (13.3)	17 (37.0)	
Living as married, N (%)	Yes	25 (80.6)	44 (95.7)	n/a
	No	6 (19.4)	2 (4.3)	
One or more children, N (%)	Yes	26 (83.9)	43 (93.5)	n/a
	No	5 (16.1)	3 (6.5)	
Tumour location, N (%)[a]	Colon	20 (76.9)	21 (53.8)	0.059
	Rectum	6 (23.1)	18 (46.2)	
Adjuvant therapy, N (%)	Yes	11 (35.5)	26 (56.5)	0.070
	No	20 (64.5)	20 (43.5)	
Stoma, N (%)	Yes	12 (38.7)	22 (47.8)	0.429
	No	19 (61.3)	24 (52.2)	
Previous life event, N (%)	Yes	8 (25.8)	17 (37.0)	0.306
	No	23 (74.2)	29 (63.0)	
Previous psychological counselling, N (%)	Yes	2 (6.5)	9 (19.6)	n/a
	No	29 (93.5)	37 (80.4)	
Social support discrepancy, mean (SD)[c]		37.2 (7.1)	39.1 (7.4)	0.270
Fear of cancer recurrence, mean (SD)[c]		11.3 (3.0)	14.0 (4.4)	***0.003***
Quality of life, mean (SD)[c]		75.3 (13.5)	66.5 (17.3)	***0.020***
Cancer-specific distress, mean (SD)[c]		9.6 (12.3)	19.9 (12.4)	***0.001***
Fatigue, mean (SD)[c]		21.7 (12.4)	27.2 (12.1)	0.060

Abbreviation: SD, standard deviation

[a]Sample size due to missing values

[b]Independent sample t test for age, social support discrepancy, fear of cancer recurrence, quality of life, cancer-specific distress and fatigue, and chi-square test for gender, education, living as married, one or more children, previous life event, previous psychological counselling and clinical variables

[c]Values at baseline

Discussion

This study evaluated the course of patient reported AD symptoms in CRC patients within the first year after diagnosis. Only a small proportion of CRC patients reported time-limited (8.6%) or persistent (1.2%) AD symptoms, almost half fluctuating symptoms, and more than one-third no MD symptoms.

Our study results indicate a low percentage of AD cases and support the evidence found in a previous study reporting an AD prevalence rate of 0.04-0.1%4. However, time since diagnosis was not reported in that study; therefore, the distinction between time-limited and persistent AD symptoms could not be made. The somewhat higher prevalence of AD symptoms in our study could be explained by the use of a screening instrument instead of a clinical interview and a younger study sample, since younger age was found to be associated with the experience of more cancer-related distress (Han, Gigic, et al., 2020). In a cross-sectional study by Tang et al. on 342 breast cancer patients, 38.6% showed AD symptoms within the first year after breast cancer diagnosis using the ADNM-20 (Tang et al., 2020), again not differentiating between time-limited and persistent AD symptoms. Here, differences between study results might be explained by a different tumor entity (breast vs. colon/rectum cancer), which was found to be a factor in the prevalence of AD (Hund et al., 2016). Further investigation of factors related to AD symptoms can be relevant to gain more insight in the transient or persistent nature of AD after cancer and to identify patients in need of psychosocial care, also after the first year post diagnosis.

The fluctuating AD and MD symptoms subgroup reported higher FCR, lower HRQoL, and higher cancer-specific distress than the no MD symptoms subgroup. A fluctuating pattern in psychological symptoms has also been observed for FCR (Custers et al., 2020) and AD symptoms (Wijnhoven et al., 2022) in breast cancer survivors. Characterizing predictors for increased psychological symptoms over time are younger age, higher education, less satisfaction with medical treatment, less ability to handle daily activities, more social support discrepancy, more neuroticism, and less optimism (Custers et al., 2020; Wijnhoven et al., 2022). In CRCS, longitudinal studies on the course of cancer-related distress showed that high distress trajectories were characterized by younger age, male gender, lower education, late disease stage, poor social support, poor socioeconomic advantage and poor preoperative functional QoL (Dunn et al., 2013; Han, Gigic, et al., 2020). The current study also found that lower HRQoL was associated with AD and fluctuating symptoms. However, demographic and clinical variables as well as social support were not associated with AD and fluctuating symptoms.

In line with studies reporting a negative emotional reaction towards cancer diagnosis (Abelson et al., 2018) and observed anxiety and depression symptoms prior to the first cancer treatment (Linden et al., 2012), our study assumed that the stressor involved in the AD symptoms was the cancer diagnosis. The DSM-5 definition describes the diverse stressor characteristics involved in AD: from a single event to multiple stressors, and recurrent or continuous stressors (American Psychiatric Association, 2013). Other phases of cancer treatment (Abelson et al., 2018) or the transition from cancer patient to cancer survivor (Garofalo et al., 2009; Han, Gigic, et al., 2020; Lim et al., 2021) could be stressful as well. This is supported by a review of qualitative studies by Lim et al., (Lim et al., 2021) who found various emotional experiences in early stage and advanced CRC. As symptoms can occur during the cancer trajectory and fluctuate over time, it is important for health care providers to monitor the emotional response to other cancer-related stressors besides the cancer diagnosis. Elevated symptoms do not necessarily warrant psychological treatment, as symptoms can diminish without interventions.

The results of this study should be interpreted with caution due to the relatively low percentage of participants who provided complete data (41.7%). This response rate might be explained by the timing of inviting patients for study participation, as their first medical treatment (i.e., surgery or start with chemo- and/or radiotherapy) took place at the same time. This can be an emotional time for patients with multiple hospital visits, and patients may be less willing to participate in a study and complete questionnaires. A strength of this study was that the study design provided a unique opportunity to observe AD symptoms in a patient population in a vulnerable medical situation after a severe stressor such as a cancer diagnosis. Furthermore, the replicability of this study might be questioned. At the time of data collection, patients with CRC symptoms were referred to the hospital by their general practitioner. Currently, the implemented national CRC screening system detects CRC even before patients experience symptoms. Finally, the present study used the HADS as an indicator of AD symptoms. By applying a range of HADS scores between cutoff points (11-14) as an indicator for AD symptoms, cases with a possible AD diagnosis reporting scores above or below that range, as demonstrated by Beek et al. (Van Beek et al., 2022) (mean HADS-T score=11.9 (SD=3.7)), might have been missed. An AD specific diagnostic interview including impairments in social or occupational functioning remains the gold standard for diagnosing AD.

Our study identified a large subgroup with fluctuating symptoms and only a small subgroup with time-limited or persistent AD symptoms. This underlines the varying emotional response intensity over time to cancer treatment and follow-up. A single

screening assessment to identify cases of AD within the first year after cancer diagnosis is not supported by our study. In case of elevated symptoms at different measurements following cancer diagnosis, a diagnostic interview would be relevant to detect those patients with AD who might benefit from psychological interventions.

Only a small proportion of the observed patients reported time-limited and persistent AD symptoms in the first year after CRC diagnosis, and almost half of them showed fluctuating symptoms. Attention should be paid to the small proportion of CRCS in which AD symptoms persist for a longer period of time.

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Chapter 4

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

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Abstract

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).

Conclusion: 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.

Background

Cancer patients may experience psychological problems [1]. 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 diagnosis [8]. Another reason for the observed variation may be that prevalence rates differ among 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, and 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 treat- ment provided by a nurse compared to other psychosocial professionals [9]. Other studies showed that patients who were younger, female, and more highly educated were more likely to accept psychological treatment [11–13]. 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 Amsterdam UMC, 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 AD [14]. 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 dis- tress 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 worker [14].

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 months [14]. 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 1 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–IIII), 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 Statis- tical 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 was 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, and 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.

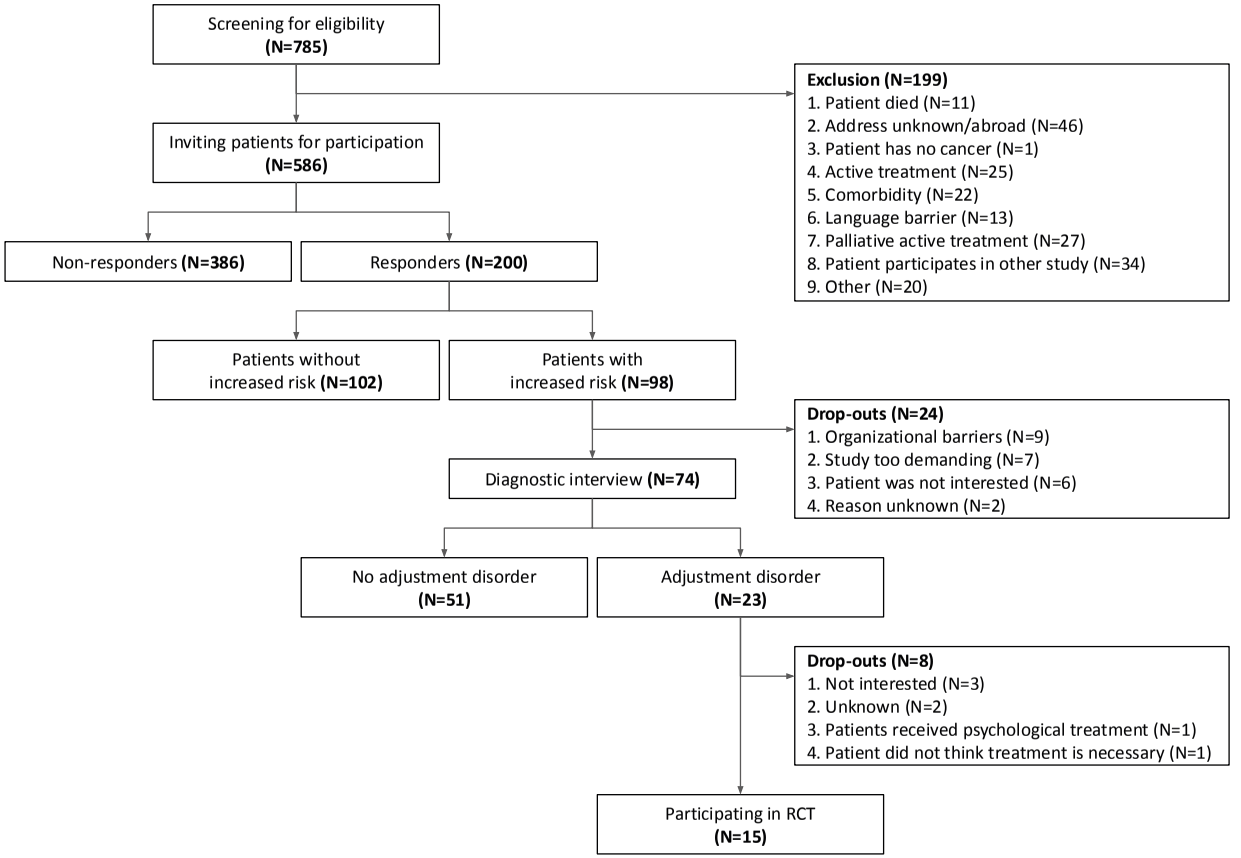

Figure 1. Flow diagram.

Table 1. Characteristics of responders and non-responders

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

Abbreviation: SD, standard deviation
Result printed in bold is significant (P<0.05)

Table 2. Characteristics study population

Characteristics	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)
Mean age (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	151 (76%)	115 (75%)	32 (51%)	19 (83%)	12 (80%)	7 (88%)
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

Table 2. Continued

Characteristics	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)
Multiple treatment	96 (48%)	73 (48%)	25 (49%)	10 (44%)	5 (33%)	5 (63%)
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 in years						
> 5	145 (73%)	119 (78%)	40 (78%)	12 (52%)	6 (40%)	6 (75%)
Psychological outcome scores mean (SD)						
HADS-T[1]	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[1]	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)[1]	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[1]	3.6 (2.8)	2.7 (2.6)	5.7 (6.0)	6.5 (1.9)	6.6 (1.5)	6.4 (2.4)
CIS[1]	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						
Practical problems (yes)	71 (36%)	44 (29%)	29 (57%)	13 (57%)	9 (60%)	4 (50%)
Family and social (yes)	30 (15%)	17 (11%)	10 (20%)	8 (35%)	5 (33%)	3 (38%)
Emotional (yes)	111 (56%)	81 (52%)	41 (80%)	19 (83%)	14 (93%)	5 (63%)
Religious or spiritual (yes)	39 (20%)	23 (15%)	12 (24%)	8 (35%)	5 (33%)	3 (38%)
Physical (yes)	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%)

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

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

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).

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

Characteristics	Patients with an increased risk who had an interview in part 2 (N=74)	Drop-outs part 2 (N=24)	P-value
Mean age (SD)	66 (11)	67 (11)	0.63
Gender			0.09
Female	41 (55%)	18 (75%)	
Married (yes/no)[1]			0.98
Yes	28 (38%)	15 (63%)	
Employed (yes/no)[2]			0.37
Yes	19 (26%)	4 (17%)	
Education (high/low)[3]			0.54
Higher education	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%)	

Table 3. Continued

Characteristics	Patients with an increased risk who had an interview in part 2 (N=74)	Drop-outs part 2 (N=24)	P-value
Hormone therapy	27 (37%)	6 (25%)	0.30
Time since diagnosis (years)			
> 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
Items on problem list (yes)			
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
Result printed in bold is significant (P<0.05)

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 4). 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 4). 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).

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 4).

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 5 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 was 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 efficient [20] and is in accordance with the Dutch guideline on AD [8]. 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.

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

	Presence of AD among all patients (N=176)		Presence of AD among patients with increased risk (N=75)		Acceptance of psychological treatment among patients with AD (N=23)
Figure 1. Variables	**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 [1.2–16.01]***	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[3]
Head and neck	0.9 [0.2–3.3]		0.4 [0.2–2.8]		0.6 [0.1–4.4]
Tumor stage (reference = I-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 scores					
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]

Table 4. Continued

	Presence of AD among all patients (N=176)		Presence of AD among patients with increased risk (N=75)		Acceptance of psychological treatment among patients with AD (N=23)
Figure 1. Variables	**Univariate OR [95%CI]**	**Multivariate OR [95%CI]**	**Univariate OR [95%CI]**	**Multivariate OR [95%CI]**	**Univariate OR [95%CI]**
Psychological outcomes scores					
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
Willingness to talk to an expert			**10.9 [2.3–51.5]***	**9.2 [1.9–45.6]***	[0.1–37.0]

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

*p-value < 0.05, **p-value < 0.01

[1]Analysis reported with 'N/A' were not applicable due to limited sample size

Results printed in bold are significant (P<0.05)

Another explanation may be the absence of clear criteria to diagnose AD, as strict diagnostic criteria for AD in the DSM-V are lacking [21]. 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 5 years prior to the study, and being willing to talk to an expert are associated with AD, while sociodemographic factors as age, sex, education, and 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 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 preferred [30]. 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 AD [10–12].

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 cancer [14]. 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 5

Diagnosing adjustment disorder in patients with cancer: evaluation of the adherence, interrater agreement and content of a guideline-based interview

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Abstract

Background: The aim of this study was to evaluate the adherence, interrater agreement and content of a guideline-based semi-structured interview for adjustment disorder (AD) in patients with cancer.

Methods: In total, 120 AD interviews with patients with cancer were performed by 9 trained psychologists. The interview contained topics related to stressors, resilience, and symptoms and complaints. Audiotaped interviews of 72 patients were available. Adherence to the interview manual was scored by two researchers independently and the average adherence was calculated per topic. Interrater agreement was calculated using Cohen's Kappa. The content of the interviews was evaluated using thematic analysis of the transcribed interviews of patients with an AD diagnosis.

Results: In the interviews, 97% of the topics were covered at least briefly and 78% of all topics were addressed at least adequately. Interviewers asked questions regarding stressors and symptoms and complaints more thoroughly compared to resilience. The interrater agreement regarding the AD diagnosis was moderate (Kappa 0.55). The content analysis showed that stressors and resilience can be additionally specified into physical, psychological, spiritual and social themes, which are relevant to explore in the context of an AD diagnosis after cancer.

Conclusion: The guideline-based interview for AD identifies problems and protective factors with adequate adherence and moderate agreement. A balanced investigation of stressors, resilience and symptoms is important for optimal clinical decision making regarding AD in the context of cancer.

Background

A growing number of patients successfully complete cancer treatment and the five-year survival rate is increasing (Netherlands Cancer Registry (NCR) Netherlands Comprehensive Cancer Organisation (IKNL)). Therefore, the psychological consequences of cancer and its treatment have become an important topic in (clinical) research (Burney, 2019; Mitchell et al., 2011). While many patients adapt well to living with cancer, there are also patients with cancer who feel unable to adjust to their new situation (Williamson & Stanton, 2018). Clinically significant emotional and behavioural symptoms in these patients can indicate the presence of an adjustment disorder (AD). According to the DSM-5 definition, AD is diagnosed when emotional or behavioural symptoms occur in response to an identifiable stressor(s) within three months of the onset of the stressor(s), and the accompanied distress is out of proportion to the severity of a stressor and/or impairments in social, occupational, or other important areas of functioning (American Psychiatric Association, 2013). An AD prevalence rate of 6% to 19% was found in mixed cancer populations when assessed with a clinical interview (Blazquez & Cruzado, 2016; Hund et al., 2016; Mehnert et al., 2014; Mitchell et al., 2011; Van Beek et al., 2022). These interviews applied the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) definition for establishing an AD.

The national Dutch guideline 'Adjustment Disorder in Patients with Cancer' was developed in 2016 in order to improve (access to) psychosocial care for patients with cancer (TrimbosInstitute, 2016). The guideline includes a diagnostic interview for AD in the acute, chronic, palliative and terminal disease phase of cancer (in short, AD interview). This interview has been applied in the context of research, detecting an overall AD prevalence rate of 13.1% in a study population of 200 patients with cancer (Van Beek et al., 2022). The AD interview contains three pillars: Stressors, Resilience, and Symptoms and Complaints. The description of the DSM-5 AD definition is also included in the AD interview manual. The interviewer enquires about burden and resilience, the ability to function in daily life and the degree of mental flexibility or rigidity within the three pillars. The interaction and coherence between the pillars combined with the DSM-5 criteria determines the diagnosis of AD. The AD interview has a semi-structured format with listed topics that could be addressed, but does not contain pre-formulated open or close-ended questions (Appendix 1) .

The accuracy of the AD interview is important to assure a high-quality diagnostic process, but this has not been established yet. Accuracy of diagnostic structured interviews for other mental disorders (e.g., somatic symptom disorder and anxiety

disorder (Axelsson et al., 2016), psychotic disorders (Martins et al., 2019), sleep disorders (Taylor et al., 2018), and AD according to the ICD-11 (Perkonigg et al., 2021)) has been investigated on two separate key aspects: interrater reliability and interrater agreement. Interrater reliability is defined as the extent to which assessors can distinguish different items on a measurement scale, meaning that it takes into account the variability and measurement error using a dimensional approach within the diagnostic tool (Gisev et al., 2013). For semi-structured interviews, it is not possible to measure the different items as there is no fixed measurement scale. Therefore, the AD interview requires an adapted evaluation further defined as 'adherence to the interview manual'. Interrater agreement is defined as the extent to which different assessors tend to make the same judgment about the rated subject, such as the categorical value of a diagnosis (i.e., yes or no) (Gisev et al., 2013). In the present study, both adherence to the interview manual and interrater agreement were investigated.

The AD diagnosis and its criteria have been discussed extensively over the last years (Bachem & Casey, 2018; Baumeister et al., 2009; Casey & Bailey, 2011; Maercker & Lorenz, 2018; O'Donnell et al., 2019; Reed et al., 2011; Stein et al., 2013; Zelviene & Kazlauskas, 2018). Criteria have been changed over time with mild to major alterations, for both DSM as well as for ICD (Bachem & Casey, 2018). Investigating AD therefore has been challenging regarding the interpretation and comparison of findings across studies. Furthermore, criticism related to AD includes the criteria being 'vague' (Baumeister et al., 2009; Reed et al., 2011) and the use of an AD diagnosis in clinical practice as a 'waste-basket diagnosis' for cases not meeting the criteria for other mental disorders (Bachem & Casey, 2018; Baumeister et al., 2009; Casey & Bailey, 2011). It has also been argued that increased distress after a life-event like a cancer diagnosis should be considered a normal stress reaction, and diagnosing a mental disorder medicalizes problems of living (Bachem & Casey, 2018; Casey & Bailey, 2011). Due to its semi-structured character, the interview provides a unique opportunity to qualitatively describe the themes that are addressed during the interview by patients and their psychologist in relation to AD after cancer. Exploration of prominent themes involved in AD after a cancer diagnosis may provide guidance in the diagnostic process of AD for professionals in the field of psycho-oncology (Bachem & Casey, 2018).

The aim of the current study was to investigate the diagnostic accuracy of a guideline-based semi-structured interview for AD in patients with cancer, by (1) investigating the adherence to the interview manual, and (2) investigating the interrater agreement regarding the AD diagnosis. In addition, the aim was to

investigate themes discussed during the interviews in patients with cancer with an established AD diagnosis to obtain more insight into which themes are addressed when AD after cancer is diagnosed.

Methods

Participants and eligibility criteria

Patients with cancer who participated in the current study were recruited in a larger study on the prevalence of AD and the reach, effectiveness, cost-utility and budget impact of tailored psychological treatment for AD in patients with cancer in a randomized controlled trial (Van Beek et al., 2022; van Beek et al., 2019). Between September 2019 and January 2020, patients were recruited at the participating hospitals in the Netherlands: Amsterdam UMC location VUmc in Amsterdam, Canisius Wilhelmina Hospital in Nijmegen, and Radboudumc in Nijmegen. Eligibility criteria for study participation were a) cancer diagnosis (all types and stages, except non-melanoma skin cancer) between July 2004 and July 2019, b) age ≥ 18 years, and c) completed primary cancer treatment with curative or palliative intent (all treatment modalities, except for endocrine therapy in breast and prostate cancer). The Medical Ethics Review Committee of the VU University Medical Centre and all participating centres approved this study (IRB00002991, 2018.524).

Procedure

Eligible patients were sent an information letter about the study by mail by their treating physician and signed informed consent to participate. Patients completed questionnaires online or with paper-and-pencil, including sociodemographic (e.g., sex, age, marital status, education level) and clinical characteristics (e.g., tumour site, tumour stage, cancer treatment, time since diagnosis), the distress thermometer (DT) (Tuinman et al., 2008) and the Hospital Anxiety and Depression Scale (HADS) (Spinhoven et al., 1997). Questionnaire data were collected using the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) system. At the start of the study, patients invited for an AD interview had 1) a HADS-total score ≥11, or 2) a DT score ≥4, or 3) reported on the DT problem list work/school/study problems, family or social problems, emotional problems or fatigue, or 4) reported the need for contact with a psychologist or social worker (yes or maybe). Due to continuing high rates of eligible participants for the interview and limited interview capacity, in December 2019 the inclusion criteria were adapted to 1) a HADS-total score ≥11, or 2) DT score ≥4, or 3) reporting the need for contact with a psychologist or social worker (yes or maybe).

Guideline-based interview for AD

After agreeing to participate in an interview, a diagnostic interview for AD was performed according to the Dutch guideline 'Adjustment Disorder in Patients with Cancer' (Trimbos Institute, 2016) by telephone (audio) or face-to-face (see Appendix 1). The topics that could be discussed were the cancer history, the current disease phase, stressors (somatic, spiritual/psychological, social), resilience (physical, autonomy, social support, spiritual meaning), the symptoms and complaints, and need for psychological care. These topics were listed on the form that the interviewer completed during the AD interview.

Interviews were performed by psychologists and psychotherapists (further called interviewers) who were registered in the expert database of the Dutch Association for Psycho-oncology (NVPO) or under supervision of a registered psychologist. All nine participating interviewers were trained to perform the interviews by completing an online training program (TrimbosInstitute, 2019; Van Beek et al., 2022). Interviewers were between 31 and 61 years of age, were all women and trained in psychology (n=2), or registered as health psychologist (n=6) or clinical psychologist (n=1). Interviewers were employed in a hospital (n=3), private practice (n=4) or a specialised psycho-oncology service (n=2) and had a median of 10 years (range 2 to 30 years) of experience in working with patients with cancer.

Data processing and analysis

In total, 120 interviews were performed. Informed consent for audiotaping was given by both the patient and interviewer for 83 interviews, of which 10 audiotapes were unavailable due to technical issues with the recording (for details see Figure 1). From the resulting 73 interviews, two separate random subsamples were selected for analysis of the adherence to the interview manual (n=19) and the interrater agreement (n=18). A third subsample with all interviews of patients who were diagnosed with AD based on the AD interview was used for the thematic analysis (n=20). Table 1 shows the demographic, medical and psychosocial characteristics of all patients with a full available audiotape of the interview (n=72). Two separate columns are included for demographic, clinical and psychosocial variables for patients with and without AD.

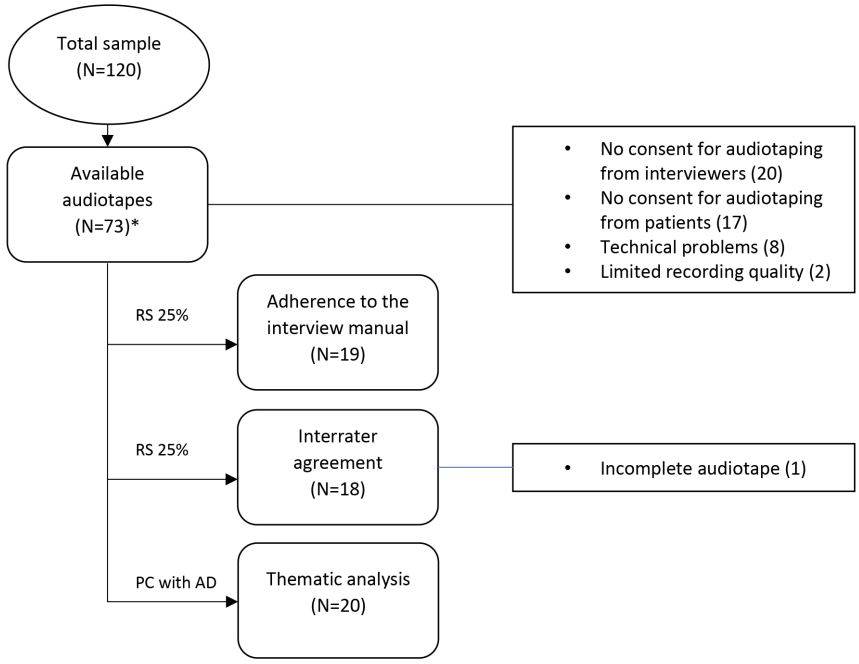

Figure 1. Selection samples for analyses.

Abbreviations: RS random sample; PC patient with cancer; AD adjustment disorder;
*Usable audiotapes (N=72)

Table 1. Demographic, medical and psychosocial characteristics of patients with cancer

	All participants (N=73)	No AD diagnosis[b] (N=53)	AD diagnosis[b] (N=20)
Sex (female)	40 (55%)	27 (51%)	13 (65%)
Age in years, mean (SD)	66.9 (9.9)	68.4 (8.2)	62.6 (12.7)
Partnered	53 (73%)	37 (70%)	16 (80%)
Education[a]			
Low	17 (23%)	13 (25%)	4 (20%)
Middle	22 (30%)	16 (30%)	6 (30%)
High	32 (44%)	22 (42%)	10 (50%)
Tumour site			
Breast	36 (49%)	23 (43%)	13 (65%)
Head and neck	16 (22%)	15 (28%)	1 (5%)
Prostate	21 (29%)	15 (28%)	6 (30%)

Table 1. Continued

	All participants (N=73)	No AD diagnosis[b] (N=53)	AD diagnosis[b] (N=20)
Tumour stage			
I - II	62 (85%)	47 (89%)	15 (75%)
III - IV	11 (15%)	6 (21%)	5 (25%)
Single treatment			
Surgery	34 (47%)	25 (47%)	9 (45%)
Radiotherapy	7(9%)	5 (9%)	2 (10%)
Multiple treatment	15 (20%)	15 (29%)	0 (0%)
Surgery + radiotherapy	4 (5%)	2 (4%)	2 (10%)
Surgery + chemotherapy	1 (1%)	1 (2%)	0 (0%)
Chemotherapy + radiotherapy	12 (18%)	5 (9%)	7 (35%)
Surgery + radiotherapy + chemotherapy			
Hormone therapy	25 (34%)	18 (34%)	10 (50%)
Time since diagnosis in years, mean (SD)	9.9 (4.6)	10.2 (4.4)	9.0 (5.3)
HADS-total score, mean (SD)	10.3 (6.7)	10.1 (6.7)	10.7 (6.8)
Distress Thermometer score, mean (SD)	5.3 (2.5)	5.3 (2.5)	5.2 (2.6)

[a]N = 71 due to missing values
[b]AD diagnosis as established by the interviewer
AD: Adjustment Disorder
HADS: Hospital Anxiety and Depression Scale
SD: Standard Deviation

Adherence to the interview manual

The analysis of the adherence to the interview manual was based on the commonly used fidelity coding method of Hepner and colleagues (Hepner, 2011). The goal of this method is to evaluate the adherence to administering a psychological intervention using a coding guide. The topics on the structured coding guide were adapted to the key topics of the AD interview; cancer history, current disease phase, stressors (somatic, spiritual/psychological, social), resilience (physical, autonomy, social support, spiritual meaning), symptoms and complaints, need for psychological care, and AD diagnosis explanation. Topics were scored as 0 (not covered), 1 (briefly covered), 2 (adequately covered), 3 (thoroughly covered) or as 'not applicable' (e.g., if establishing the AD diagnosis was postponed by an interviewer for supervision consultation) (Hepner, 2011).

In absence of clear guidelines for sample size, and for reasons of feasibility, the analysis of the adherence to the interview manual was conducted on a randomly selected subsample of 25% (n=19, subsample adherence). Stratification for the

interviewer and institution of the interviewer was applied selecting at least one interview per interviewer and institution to cover possible differences in interview techniques between interviewers. The duration of each interview was noted, and the key topics were scored by two researchers independently (LW and LZ). Per topic, the adherence to the interview manual was determined: inadequate (a score of 0 or 1) or adequate (a score of 2 or 3). In case of an unclear topic assessment a third researcher (JP) was consulted. For all interviews, the average percentage of the covered topics was calculated, and the median coverage was determined. The involved researchers had a master's degree in biomedical sciences or cognitive neuropsychology, had the same interview training as the interviewers and were experienced in patient communication. The third researcher was a clinical psychologist with extensive experience with patients with cancer.

Interrater agreement

To gain insight in the interrater agreement regarding the AD diagnosis, another subsample including 25% (n=19) of all interviews was selected randomly. After exclusion of one interview due to premature termination of the recording of the interview, 18 AD interviews (subsample agreement) were used for interrater agreement analysis. The feedback on the AD diagnosis by the interviewer was removed from the audiotapes, after which the adjusted audiotapes were analysed by an assessor, who independently assessed whether an AD diagnosis was applicable. The assessor was a psychiatrist with extensive expertise in AD after cancer, who received substantial training in mental disorder diagnostics, was involved in the development of the Dutch guideline and had the same interview training as the interviewers. The assessor was blinded to the interview outcome and did not know the names of the involved interviewers. In case of an indecisive assessment by the assessor, a second researcher (JP) was consulted. The percentage of agreement between the interviewer and assessor was calculated and corrected for agreement occurring by chance (Cohen's Kappa) and interpreted (<0.00 as indicating no agreement, 0.00–0.20 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement, and 0.81–1.00 as almost perfect agreement) (Landis & Koch, 1977).

Thematic analysis

All 20 audiotapes of the patients who were diagnosed with AD following the AD interview were transcribed verbatim. Transcripts were coded independently by two researchers (LW and LZ) using Atlas.ti. Coding of stressors, resilience and symptoms were performed according to the theoretical framework analysis (Anfara Jr & Mertz, 2014). Codes were linked to the line(s) related to the categories. Lines could be selected for

multiple codes. In case a code did not fit in one of the categories, a separate category was created. The two researchers met regularly to clarify the meaning of codes and to further refine the coding system. The codes were explored on possible relationships, related concepts or subthemes and bundled in a theme (axial coding). Codes could belong to multiple themes. The two researchers met to solve discrepancies in the created themes. The data were charted and interpreted according to the theoretical framework, combining an inductive approach with placing the retrieved (sub)themes into the structure of the three pillars of the AD interview. The coding process, theme recognition and interpretation of the data were discussed with other team members (JC, LK and JP) during the analysis of all transcripts. Representative quotes were selected to illustrate emergent themes. All researchers involved in the coding and data-analysis had sufficient knowledge and experience in performing qualitative research.

Results

Adherence to the interview manual

The average duration of an AD interview in the adherence subsample (n=19), without the introduction to the interview, was 31 minutes (range 12-70 minutes). The percentages per covered topic are shown in Table 2. In the interviews, 97% of the topics were covered at least briefly and 78% of all topics were addressed at least adequately. In general, social stressors were covered briefly, and the cancer history, stressors in general and the experience of symptoms and complaints were thoroughly covered. Overall, the pillars Stressors and Symptoms and Complaints were discussed more thoroughly than the pillar Resilience.

Table 2. Adherence to the interview manual (N=19)

	Coverage			
Interview topic	**Not covered**	**Brief**	**Adequate**	**Thorough**
1 Cancer history, N (%)	0 (0%)	0 (0%)	4 (21%)	***15 (79%)***
2 Current disease phase, N (%)	0 (0%)	4 (21%)	***12 (63%)***	3 (16%)
3 Stressor(s), N (%)	0 (0%)	3 (16%)	6 (32%)	***10 (53%)***
· somatic, N (%)	0 (0%)	4 (21%)	5 (26%)	***10 (53%)***
· spiritual/psychological, N (%)	0 (0%)	1 (5%)	4 (21%)	***14 (74%)***
· social, N (%)	2 (11%)	***8 (42%)***	6 (32%)	3 (16%)

Table 2. Continued

	Coverage			
Interview topic	**Not covered**	**Brief**	**Adequate**	**Thorough**
4 Resilience, N (%)	0 (0%)	3 (16%)	***9 (47%)***	7 (37%)
· physical, N (%)	0 (0%)	5 (26%)	***7 (37%)***	7 (37%)
· autonomy, N (%)	3 (16%)	6 (32%)	***3 (16%)***	7 (37%)
· social support, N (%)	0 (0%)	4 (21%)	***9 (47%)***	6 (32%)
· spiritual meaning, N (%)	1 (5%)	5 (26%)	***8 (42%)***	5 (26%)
5 Symptoms and complaints, N (%)	0 (0%)	0 (0%)	6 (32%)	***13 (68%)***
6 Need for psychological care, N (%)[a]	0 (0%)	3 (19%)	***10 (63%)***	3 (19%)
7 Adjustment disorder diagnosis and explanation, N (%)[b]	3 (17%)	2 (11%)	***6 (33%)***	7 (39%)

[a]Inquiry about the need for psychological care was not applicable in 3 interviews.
[b]AD diagnosis was postponed for supervisor consultation by the interviewer.
Median: ***bold underlined*** values

Interrater agreement

For the agreement subsample (n=18), Cohen's Kappa was 0.55 (moderate agreement). There was agreement for 3 interviews with an AD diagnosis and 12 interviews without an AD diagnosis (83%). Disagreement between the assessor and interviewer was found for three interviews (17%), in which either the assessor evaluated an AD diagnosis and the interviewer concluded no AD diagnosis (n=1) or the other way around (n=2). Review of these interviews revealed that differences between the interviewer and assessor concerned the extent to which psychological symptoms were related to cancer, the severity of symptoms and the adequacy of the coping strategy of the patient.

Thematic analysis AD interviews

Table 3 presents a summary of the themes discussed in the interviews of 20 patients with cancer who were diagnosed with AD. These themes were mentioned by patients and interviewers and structurally organised within the pillars Stressors, Resilience, and Symptoms and Complaints. Interviewers additionally enquired general information of the patient with cancer, although this was not specifically indicated in the interview manual. This information was divided in six themes: (1) the medical treatment of cancer, i.e., experiences regarding the diagnostic, treatment and follow-up phase, the experienced support from the medical specialist and genetic testing; (2) (para)medical care, i.e., physical therapy or oedema therapy; (3) personality traits, i.e., perfectionism, analytic thinking, perseverance; (4) other life-events, i.e., death

of a relative (due to cancer) or divorce; (5) previous psychological counselling, i.e., success of previous help for psychological problems in general or related to cancer; and (6) request for psychological help, i.e., the need for help and the topic of the request for help (acceptance of fatigue, dealing with body insecurities).

Table 3. Themes discussed during the interview for Adjustment Disorder in patients with cancer

Stressors	**Subtheme**	**Examples**
Physical	1. Physical consequences of cancer (treatment) 2. Internal triggers	1. Fatigue, physical tension, body changes 2. Bodily signals leading to e.g., uncertainty, anxiety, negative thinking
Psychological & spiritual	1. External triggers 2. Negative thoughts 3. Worries about sexuality/intimacy 4. Frame of reference	1. Social interaction, hospital setting 2. Thoughts regarding cancer recurrence and the impact of cancer on quality of life 3. Limited/ineffective strategies to handle sexuality and intimacy issues 4. Anxiety / Stress after life-events, relating cancer to other (previous) life-events
Social	1. Social activities 2. Experiences with social support 3. Work 4. Experiences with medical treatment	1. Limited participation (burdensome, choosing between activities) 2. Discrepancies in perceived and received social support 3. Limited work capacity, stressful return to work 4. Dissatisfied and difficulties with interacting with medical staff
Resilience	**Subtheme**	**Examples**
Physical	1. Residual physical symptoms 2. (para)Medical treatment for physical symptoms 3. Healthy lifestyle adaptations	1. Adjusting to physical changes 2. Professional medical and non-pharmacological support, (para)medical care helps normalise symptoms 3. Change in health behaviours (e.g., diet, exercise, smoking cessation)
Autonomy	1. Sense of control 2. Adaptive distraction seeking 3. Coping resources	1. Self-direction in medical treatment and other life domains 2. Proactively engaging in activities such as hobbies 3. Practical and mental strategies to deal with challenging situations
Social support	1. Emotional support 2. Practical support	1. (changes in) Relationships and communication 2. Receiving help from others (e.g., housekeeping)

Table 3. Continued

Spiritual meaning / Existential[a]	1. Purpose and meaning in life 2. Changing priorities	1. Questioning meaning of life, adjusting future activities 2. Prioritizing activities that give meaning and enjoyment (participation choices, adjusting work activities)
Psychological[a]	1. Acceptance 2. New perspectives on life	1. Coming to terms with limitations, going through a recovery process after cancer treatment 2. Putting cancer in perspective with other life events, toning-down of cancer
Symptoms and complaints	**Subtheme**	**Examples**
Physical[a]	1. Fatigue 2. Pain 3. Sexual dysfunction and intercourse 4. Other physical symptoms of cancer treatment	1. More, different and unexpected fatigue 2. Polyneuropathy after radiation, pain after exercise 3. Reduced libido, less intercourse 4. Reduced bodily functions (senses, musculoskeletal system, digestive and urinary tract)
Psychological[a]	1. Behavioural/ personality changes 2. Altered body confidence 3. Awareness of body signals 4. Mood 5. Fear and worry 6. Emotional reactivity 7. Altered memory and concentration	1. Less spontaneity, less patience 2. Distorted self-image, loss of trust in own body 3. More alertness, difficult to distinguish normal from serious body signals 4. Depression symptoms, feeling down, apathy 5. Fear for medical tests, fear of cancer recurrence, rumination 6. Feeling overwhelmed with emotions, irritated or angry more easily, restlessness 7. Memory problems, decreased focus, confused thinking
Social[a]	1. Diminished participation 2. Difficulties in sharing of emotions	3. Withdrawal from friends, decreased social network 4. Not talking about fear of cancer recurrence, depressed mood

[a]The subthemes existential and psychological resilience are not included in the interview manual, and the subthemes physical, psychological and social symptoms and complaints are not distinguished in the interview manual

Stressors

The pillar Stressors is divided into three major themes: physical, psychological/ spiritual and social stressors. Two subthemes of physical stressors were identified. The first subtheme physical consequences of cancer (treatment) involved difficulties relaxing the body and being self-conscious or feeling insecure about the body.

Patients described a general increased body tension and that body changes have an impact on well-being. The second subtheme was internal triggers to physical changes. Patients described that the experience of body signals (e.g., pain) can lead to anxiety, uncertainty or imagining the worst-case-scenario about the cancer returning.

> *But I just notice that every time you call the doctor, even if you have something, ... Every time you think, is it something? That makes you feel very insecure. (Subtheme internal triggers to physical changes)*

Four subthemes were identified in the context of psychological and spiritual stressors. First, patients mentioned experiencing external triggers. For example, being reminded of their experiences with cancer during social conversations or visiting the hospital caused stress. Second, negative thoughts related to cancer occupied patients, for example 'If the cancer returns, the consequences will be worse'. Third, sexuality and intimacy were important topics for patients not knowing what to do when sexual functioning is limited or have difficulties discussing decreased intimacy with a partner. The fourth subtheme frame of reference described the cancer experience resulting in an increased stress vulnerability when experiencing other life-events. Patients mentioned that previous life-events also had or still have a major emotional influence.

> *And I also sometimes think like, in those years when I had breast cancer, a year before my father-in-law passed away very unexpectedly, he died... It's not only just that breast cancer, as I always tell people. It's also… You go through a lot of things in life sometimes, a lot in a short period of time. (Subtheme frame of reference)*

Four subthemes were identified as social stressors. First, participation in social activities was described to be more burdensome than before the cancer. Additionally, due to limited available energy for social activities, patients mentioned missing out on activities that they want to engage in. The second subtheme related to social support from others, when the amount or kind of received support did not meet the expectations of patients.. Third, work was described as an important social stressor, as returning to work or being unable to work after cancer treatment can be physically and mentally challenging. The fourth subtheme involved experiences with medical treatment by medical professionals during cancer treatment and follow-up. Patients mentioned disappointment or anger due to insufficient information about the cancer treatment or discrepancies between the perceived and received treatment from the medical team, also after the completion of the cancer treatment.

I was working at the time, but that was one of the things that the colleagues… If they came by, then the conversation was only about that (cancer), and I actually got sick of it all. (Subtheme work)

I would have preferred other support like doing fun things with me. Yes, I did have all the treatment of course, but it is not that I didn't realize it. But it had to stop there, too. I wanted to, I actually just wanted to move on. (Subtheme social support from others)

Resilience

The pillar Resilience is divided into four major themes: physical resilience, autonomy, social support and psychological resilience. Physical resilience can be divided into three subthemes. First, the subtheme adjustment to residual physical symptoms caused by cancer or its treatment was described by patients. Some patients found it difficult, some got used to living with residual symptoms and others even forgot that they had symptoms. In the second subtheme the role of the (para)medical professional providing care was described. The effect of this care can be supporting, but also the patient-healthcare provider interaction was mentioned to have an influence on the experience of cancer care. Lastly, patients described implementing healthy lifestyle adaptations, depending on what they find important. For example, some patients changed their diet or quit smoking, others started to exercise individually or with guidance of a physical therapist. These choices were made to positively affect health in general or to reduce physical complaints.

Continuing to exercise. Right now it's to get rid of those symptoms that I have now. But those things are just all to somewhat change your lifestyle. (Subtheme healthy lifestyle adaptations)

Interviewer: How do you adjust to that?
Participant: Taking yourself into consideration the best that you can and trying to arrange work and family life so that it does remain acceptable. Only in my work, there are ups and downs. (Subtheme adjustment to residual physical symptoms)

Autonomy as a resilience theme can be divided into three subthemes. First, patients described the sense of control during their medical treatment or in life in general as an important subtheme. Patients described the decision-making process regarding surgery, radiotherapy and medication, and whether they felt their input was taken into consideration. Second, adaptive distraction seeking was described as being

helpful to deal with physical and mental complaints. Regarding the third subtheme, different resources for coping with negative consequences of cancer have been mentioned. Examples were having an active and positive attitude towards challenges in life, adapting physical load to the capacity of the body, avoiding negative influences on mental health by taking care of physical complaints and prioritizing own needs and desires rather than those of other people.

> *I hike a lot. I've decided to go on big walks with a friend since a few months. You know, that way I can clear my head. (Subtheme adaptive distraction seeking)*

Another resilience theme is social support that can be divided into emotional support and practical support. Patients mentioned that emotional support provided by a partner, family, friends and others can be helpful. It was also mentioned that talking about the consequences of cancer and the healing process after cancer is not easy at times. Other patients described that it can be confronting to talk about cancer or express that they do not want to talk about cancer anymore. This is described as influencing the quality of relationships. The second subtheme practical support is defined as the help from others, for example help with cleaning the house.

Spiritual and existential meaning was mentioned as a resilience theme including two subthemes. First, the purpose and meaning in life was mentioned to be questioned. Patients described reflecting on their role in life, and what activities no longer contribute to that role. Furthermore, patients mentioned that engaging in routine activities is no longer given and plans for the future are adapted based on the new situation after cancer treatment. Second, the experience of cancer was described as evoking priorities in choices. Patients described an altered awareness of gratitude and enjoyment of life. Importance of work or personal activities were also found to be altered.

> *But also because of the cancer the second time around, I did enjoy the things that were going well... There are a lot of people who can't do that anymore. I enjoy all kind of things more intensely, all kind of very ordinary things too. (Subtheme priorities in choices)*

Lastly, the theme psychological resilience is distilled among the codes, which was not explicitly defined in the interview manual. This theme contains two subthemes, namely acceptance and putting matters into perspective. First, patients described the process of acceptance of having had cancer and the physical limitations that

follow. Whether and how this process has taken place differed among patients. Second, strategies were mentioned to put matters into perspective and to cope with the situation after cancer. Examples are applying cognitive reframing to compare the cancer experience to other experiences or comparing own problems to the problems experienced by other people or trivializing the experienced problems.

> *I would indeed like to know how I can deal with this fatigue. What else can I do, or what else can I do to improve it, or maybe come to terms with it and learn to live with it, or something like that. Because it may be that I just have to live with it, with something like that. (Subtheme acceptance)*

> *You are still missing a breast. And although I always say that if I have to get cancer again, I'll opt for getting breast cancer again. But yes, the situation is not really pleasant... I have accepted it to the point that I even don't wear a prosthesis anymore. (Subtheme put matters into perspective)*

Symptoms and Complaints

Patients with cancer reported a variety of symptoms and complaints. These were divided into the themes: physical symptoms, psychological symptoms and social changes. This division was not explicitly included in the interview manual.

The experienced physical symptoms were described to be caused by cancer and its treatment, mainly fatigue, pain, sexual dysfunction and other reduced body functions (e.g., senses, musculoskeletal system, digestive and urinary tract). Notably, the experience of fatigue was mentioned to be of physical (rather than psychological) nature by the patients.

The described psychological symptoms can be divided into seven subthemes. Behavioural and personal changes were experienced by the patients themselves or by significant others. Additionally, a decrease of body confidence, for example related to breast amputation or erectile dysfunction, and an increase in awareness of signals of the body experienced as 'good' or 'bad' were described. A change in mood, feeling down or apathy were mentioned. Furthermore, fear during and after the cancer trajectory, fear of cancer recurrence and worrying about the impact that the consequences of cancer or the recurrence of cancer on the environment were described affecting psychological well-being. Also, emotional reactivity was described by patients as being agitated more easily and feeling overwhelmed by emotions that were not effectively contained or processed. Lastly, activities that

require memory and concentration were described as being a challenge in for example working situations.

The theme social changes were regarding two subthemes. First, a decrease in diminished social participation and a decrease in the number of people involved in the social network can result in feeling lonely and being less engaged in social context. Second, talking about the emotional reaction on having had cancer with the people involved in the life of patients, can be sometimes perceived as difficult by patients.

> *I can handle more things for a longer period now. But it does take a lot more effort than before in terms of concentration, in terms of planning, when do I do what… (Subtheme psychological symptoms)*

Discussion

This study evaluated the accuracy and content of a guideline-based semi-structured interview for AD in patients with cancer. The adherence to the interview manual was adequate and interrater agreement was moderate. The content analysis showed that the pillars Stressors and Resilience can be further specified into physical, psychological, spiritual and social themes, providing a useful guidance to explore the context of patients with cancer related to an AD diagnosis.

The adherence to the interview manual was adequate, though topics related to Stressors and symptoms and complaints appeared to be discussed more thoroughly by interviewers than topics related to resilience. In general, clinicians performing diagnostic interviews are more familiar with questions regarding stressors and symptoms as these kind of questions are part of structured interviews like the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2016) and Composite International Diagnostic Interview (CIDI) (Kessler & Ustun, 2004). The interview manual for AD however indicates to inquire about resilience in addition to symptoms. Resilience can be a protective factor, as resilience can mediate between stressors and symptoms, resulting in less symptom burden despite the exposure to a stressor or life event (Trimbos Institute, 2016; Ye et al., 2017). It is therefore advised for psychologists to perform the AD interview as a balanced investigation of stressors, resilience and symptoms and complaints, and to consider profound questioning on all topics to be equally important. This could be emphasized more explicitly in the training of performing the AD interview.

Our evaluation of the AD interview showed a moderate interrater agreement regarding the AD diagnosis in patients with cancer (Kappa 0.55). Evidence for interrater agreement regarding the AD diagnosis is scarce. Perkonigg et al. (Perkonigg et al., 2021) found high adjusted Kappa (0.81) for an AD diagnosis in a test-retest study in adolescents and adults attending university using the Diagnostic Expert System for mental disorders with the AD definition according to the ICD-11 (DIA-X-5), which was applied in a later study in patients with prostate cancer, head and neck cancer and other tumour types (Perkonigg et al., 2021). Differences in the interrater agreement between that study and the present study might be explained by the semi-structured versus structured way the diagnostic interviews were performed. An open dialogue can result in more variability in answers and the interpretation of those answers compared to close-ended questions (Mueller & Segal, 2014). Notably, the present study used the DSM-5 classification (American Psychiatric Association, 2013) and Perkonigg et al. used the ICD-11 classification (World Health Organization, 2019). These two classifications differ in criteria for AD symptoms. Furthermore, in our study only participants who scored above the cut-off on screening questionnaires were invited for the interview, whereas in the study by Perkonigg participants were not pre-screened. Also, in the test-retest design of the study by Perkonigg, participants were interviewed twice, and in our study participants were interviewed once and assessed twice. Recall bias in the first design, question selection variability between interviewer and assessor and screening of cases at risk for AD in the second design could have influenced the results differences. Another study described the structured Diagnostic Interview for Adjustment Disorder (DIAD) based on DSM-IV that was developed in 2012 (Cornelius et al., 2014), but the interrater agreement of this interview has to our knowledge not yet been investigated nor has the interview been applied in other studies. It would be beneficial for clinical practice to investigate which interview would be most suitable to diagnose AD in patients with cancer and in the general population. It is also important for future studies to enhance the comparability between studies in order to generate more rigorous evidence on, among other things, screening and diagnosing of AD (Morgan et al., 2022).

This first analysis of the content of the interviews revealed that the three pillars Stressors, Resilience and Symptoms and Complaints and their specific (sub)themes were relevant to the context of patients with cancer with AD. As outlined in the interview manual, all Stressor related themes (physical, psychological/spiritual, and social stressors) were inquired by interviewers. All Resilience related themes regarding physical, autonomy, social support, and spiritual meaning/existential themes were addressed by the interviewers. Additionally, psychological resilience

was addressed, although this is not incorporated in the manual. It is important to recognise that these results focus on themes and subthemes related to stressors, resilience and symptoms and complaints in a sample of breast cancer, prostate cancer and head and neck patients with a cancer diagnosis up to 15 years ago. Themes relevant for patients with AD in the current study who were diagnosed with cancer up to 15 years ago could be different for other samples such as patients recently diagnosed with cancer. Also, relevant (sub)themes could be dependent on tumour type specific stressors that are experienced by patients, like having a stoma in for example colorectal cancer (Abelson et al., 2018) or a mastectomy in breast cancer (da Silva & dos Santos, 2010). Our results can provide valuable input for further elaborating other themes and subthemes of the interview manual for diagnosing AD after cancer and for diagnosing AD in general. This could contribute to a more uniform performance of an AD interview.

Limitations

As far as we now, this is the first evaluation of the AD interview manual, so comparing results with other studies is only partially possible. This study was part of a larger study on the AD prevalence after cancer (Van Beek et al., 2022; van Beek et al., 2019), therefore results are biased towards the characteristics of the sample. During this study, inclusion criteria for participation in the interview were adapted, excluding the participants who solely reported physical complaints. This could have contributed to a selection bias with participants who did not report psychological symptoms during the screening procedure but who would meet the criteria for AD after cancer. In addition, not all psychologists gave consent for recording of the interviews, which could also induce bias.

Another limitation is that the interview was performed in a research setting, and interviewing in clinical practice may proceed differently. The average duration of an interview was significantly shorter than a regular intake consultation in clinical practice. Reimbursement was offered for one hour, including the interview and the diagnostic report, and most of the interviews were held via telephone limiting non-verbal communication. Interviewers were instructed to focus in the interview on whether symptoms of AD were related to cancer and to not go into detail when other stressors from different life-events were mentioned. The research setting could have therefore induced bias.

Conclusion

The guideline-based interview for AD adequately identifies the problems and protective factors of patients after cancer diagnosis and/or treatment with moderate reliability and provides professionals with detailed guidance to diagnose AD. Themes regarding stressors and resilience are advised to be equally addressed.

Clinical implications

Recognising aspects contributing to both stressors and resilience in the AD interview is of interest for professionals to optimise clinical decision making. This contributes to accurately diagnosing AD, as well as proactively addressing and potentially strengthening protective factors (Fletcher & Sarkar, 2013). It is necessary for an optimal performance of the interview to be trained in balancing between both stressors and protective factors to obtain a substantiated AD diagnosis. Accurate AD diagnostics is important to recognise the problems patients with cancer face and can give direction to suitable interventions, such as participating in support groups, e-health interventions or other psychological treatments.

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Appendix 1: Interview Form

1. Diagnostic form

Name patient: Date:

DSM-5 classification

Main classification: Adjustment disorder, specified with depressed mood, with anxiety, with mixed anxiety and depressed mood , with disturbance of conduct, with mixed disturbance of emotions and conduct, unspecified

Other classification (when applicable): .....

GAF- score (when applicable): .....

Problem Severity □ Mild □ Moderate □ Severe

Complexity □ Absent □ Limited □ High

Disease phase Acute, chronic or palliative		
Stressors a. Physical b. Psychological and spiritual c. Social		
Resilience a. Physical b. Autonomy c. Social support d. Spiritual meaning	**A. Physical**	0 1 2 3 4 5 6 7 8 9 10
	B. Autonomy	0 1 2 3 4 5 6 7 8 9 10
	C. Social support	0 1 2 3 4 5 6 7 8 9 10
	D. Spiritual meaning	0 1 2 3 4 5 6 7 8 9 10
Symptoms Complaints and symptoms		
Would the patient want psychological treatment for his/her complaints? **Yes / No**		

2. Descriptive diagnosis

Name patient:	**Male/female**	**Age:…….year**	**Other characteristics:**

Has……..…….…..……. (type of cancer)

Specify the medical treatment for cancer he/she has had:

……..
Stage (if the patient is familiar with this information): I / II / III / IV

Is currently in the: acute / chronic / palliative / terminal phase

Recently he/she has in increasing amount of problems with "<psychological complaints>" … after…
Explore: luxating, sustaining, vulnerability and protective factors
Consider: coping mechanism, resilience vs. burden, personality traits, social isolation, carrying burden due to illness or complications in diagnostic phase (patients delay or late recognized or acknowledged somatic disease(s))

Additionally mention psychological/psychiatric history

Diagnosis: **no / yes** adjustment disorder

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Chapter 6

General Discussion

Introduction

The overall aim of this thesis was to obtain insight into (1) the presence and course of symptoms of AD, (2) the prevalence of AD and (3) themes relevant to diagnose AD after cancer treatment. Studies of this thesis were performed among patients with cancer and cancer survivors with different time intervals since cancer diagnosis within the complex context of psycho-oncological care. This general discussion elaborates on the main findings and compares the results with current knowledge and clinical care within the field of psycho-oncology. To improve readability for this discussion, unless specified, both groups are further called 'cancer survivors', in line with the suggestion of Marzorati and colleagues (Marzorati et al., 2017). Based on the overview provided in this general discussion, directions for future research and clinical implications will be given.

In summary, regarding *the presence and course of symptoms of AD*, the longitudinal study in breast cancer survivors **(Chapter 2)**, who were within 5 years post-diagnosis and were followed for one year, showed that most women are resilient after cancer diagnosis and treatment with no symptoms of a mental disorder (MD). Some survivors have experienced continuous symptoms of AD, but most had a fluctuating course of symptoms of AD during the period of one year, indicating the presence of psychologically challenging times or events but also resilience to recover afterwards. A somewhat similar pattern was observed in a sample of patients with colorectal cancer **(Chapter 3)**, who were followed for one year after their cancer diagnosis. In this study a substantial proportion of patients showed no symptoms of a MD and the majority of patients showed fluctuating course of symptoms over time. Remarkably, only a small proportion of patients had symptoms of AD resolving (time-limited symptoms of AD) or persisting over time (persistent symptoms of AD), which might indicate that experiencing psychological challenges after a cancer diagnosis may not necessarily be as steady and directly related to the stressor cancer.

Regarding the *prevalence of AD* when assessed with a guideline-based diagnostic interview, the results of **Chapter 4** showed that one out of 6 (13% to 15%) patients with various cancer diagnoses up to 15 years following the cancer diagnosis was diagnosed with an AD. Patients who were actively employed and with a shorter time since diagnosis were more likely to be diagnosed with AD. Of those diagnosed with AD, 65% of the patients were willing to receive psychological treatment. The guideline-based diagnostic interview that was used to assess the prevalence of AD, was applied adequately as investigated in **Chapter 5**, and showed moderate interrater agreement regarding an AD diagnosis. Themes and subthemes related to

stressors, resilience, symptoms and complaints were relevant to describe the context of a patient with cancer and AD, where interviewers elaborated more on stressors and symptoms and complaints than on resilience.

Screening for symptoms of AD

Two topics should be considered regarding the presence and course of symptoms of AD. First, the variability in study results on the presence of symptoms of AD in cancer survivors is large. In **Chapter 4**, 49% of the patients in the ADJUST-study were identified at risk for AD based on the broadly defined criteria of a total Hospital Depression and Anxiety Scale (HADS) score of ≥11 or Distress Thermometer of ≥4 or the need to talk with a psychologist or social worker (Spinhoven et al., 1997; Tuinman et al., 2008). This percentage is higher compared to two studies investigating a similar sample of patients with cancer finding 30% of cases at risk for AD using the Patient Health Questionnaire-9 (Hund et al., 2016; Mehnert et al., 2014) and 39% in patients with breast cancer using the Adjustment Disorder New Module-20 (ADNM) (H. Y. Tang et al., 2020). The variability in percentages could be explained by differences in the goal of the studies, were in our study the goal was to select cases for clinical interviewing on presence of AD and psychological treatment for AD, whereas the other studies aimed to detect cases with symptoms of AD. Additionally, the screening questionnaires used in all studies have their own psychometric properties, and different sensitivity and specificity to detect cases at risk for AD. Before a specific AD screening questionnaire was available, various other questionnaires like the Social Subscale of the Functional Assessment of Cancer Therapy–General (Kirsh, McGrew, Dugan, et al., 2004), HADS (Razavi et al., 1990), and the Zung Depression Scale (Passik et al., 2001) served as screening questionnaires for an indication for AD in patients with cancer but were not developed to screen for AD initially. Till 2004, available screening instruments appeared to be useful in predicting the presence of any MD and not just AD (Kirsh, McGrew, & Passik, 2004). Over the last twenty years, several research groups have developed their own screening questionnaires to identify cases at risk for AD, for example the One-Question-Interview (Akizuki et al., 2003) and the ADNM (Maercker et al., 2007), and none have been widely implemented in cancer research. Introducing a widely accepted AD screening questionnaire would be beneficial for the comparison between study results in future studies, which is in line with the identified research gap formulated by Morgan and colleagues (Morgan et al., 2022). The ADNM appears to show the most prospects on psychometric properties (H. Tang et al., 2020) and validity in patients with cancer (Harris et al., 2023) and could provide a more universal method to investigate the presence of symptoms of AD after cancer. As some studies reported prevalence rates of AD as determined by questionnaires whereas a prevalence rate of AD can only be determined using a clinical interview,

it is additionally recommended to explicitly discriminate 'symptoms of AD', 'positive AD case' or 'case at risk for AD' from 'AD diagnosis'.

The second important topic related to symptoms of AD is that most patients and survivors appear to react resilient over time to the stressor of a cancer diagnosis and show no symptoms of an MD or fluctuating symptoms. **Chapter 2** and **Chapter 3** demonstrate that only a small percentage of the cancer survivors show symptoms of AD in line with the definition of time-limited and persistent symptoms of AD. The occurrence of fluctuating symptoms after a cancer diagnosis has also been demonstrated for more specific psychological responses like fear of cancer recurrence (Custers et al., 2020). This could imply that, during a period of a year, fluctuating psychological symptoms occur more commonly than symptoms of a MD (persistent AD, depression, or anxiety). It is important for clinicians to be aware that it is common for symptoms to fluctuate over time in response to stressful events, but that the majority of patients can adequately manage themselves. With this in mind they can determine the appropriate follow-up of an increased score on a screening questionnaire. In general, the purpose of screening by means of a questionnaire is to identify cases for a more thorough assessment who might benefit from psychosocial health services (Vodermaier et al., 2009). Selecting cases with higher scores on screening questionnaires can be beneficial for clinical and research resources (i.e., finances and time), and reduces the number of clinical interviews which can be found burdensome for patients. As demonstrated by our longitudinal studies, it would be more useful and resourceful for patients and clinicians to not include external resources like professional support for a diagnostic interview or psychological treatment, immediately after a single elevated score. While being aware of persistent symptoms or symptoms of another mental disorder or suicidal ideation (Gradus et al., 2010) and making use of the already available support and resources (e.g. self-management strategies, e-health interventions, and support groups) it might be more appropriate to actively monitoring the patient's resilience and abilities to adjust and recover from symptoms.

Summarizing, the prevalence of cancer survivors with symptoms of AD varies. On a cross-sectional level, many cancer survivors show increased symptoms at some point in time. However, longitudinal screening for symptoms of AD seems needed given the large group of patients showing a fluctuating course of symptoms. Longitudinal screening could be beneficial in detecting those survivors in need of psychosocial support.

Diagnosing AD

To understand how many cancer survivors suffer from significant adjustment problems, it is important to take a closer look at the AD diagnostic interview used to determine the prevalence of AD after cancer. In **Chapter 4**, the guideline-based semi-structured interview (TrimbosInstitute, 2016) was applied during the ADJUST-study in 200 cancer survivors with a cancer diagnosis up to 15 years ago. The interview used the AD definition formulated in the fifth edition of the DSM (DSM-5) (American Psychiatric Association, 2013) and was divided into the pillars (1) Stressors, (2) Resilience and (3) Symptoms and Complaints. The interview was moderately reliable to establish an AD diagnosis, and adequately performed by interviewers (**Chapter 5**). Using this interview, an AD prevalence of 13% was found, which is similar to the results of two key studies investigating the prevalence of AD in patients with cancer. The first major study is a systematic review and found an AD prevalence of 15% in palliative care settings and 19% in oncological and haematological settings (Mitchell et al., 2011). This systematic review reported that it included various structured, semi-structured, and clinical interviews, but this is debatable as before its publication in 2011, no interview for AD had been widely adopted or validated in the field of (psycho-)oncology. In the second major study, a specified description of the applied interview was included detecting a 4-week AD prevalence of 11% in patients with cancer from in- and outpatient care facilities. In this interview, questions were added to the Composite International Diagnostic Interview for Oncology (CIDI-O) regarding DSM-IV AD criteria (distress not meeting another axis I disorder and not persisting longer than six months after the occurrence of the stressor) (Mehnert et al., 2014). However, the validity of this interview was not evaluated. So although prevalence rates are comparable between these studies diagnostic assessment methods vary per study and methods are sometimes designed for a single study specifically, lacking a gold standard AD diagnostic interview.

The use of different diagnostic methods to investigate AD prevalence can be explained by the absence of a valid diagnostic interview up till 2014. Before that time, the diagnosis AD was common in clinical practice of mental health institutions (Zelviene & Kazlauskas, 2018), so there was a growing need to diagnose AD by means of a reliable diagnostic interview. This has led to the development of the Diagnostic Interview Adjustment Disorder (DIAD) in 2014. The DIAD is based on partly adjusted operationalized DSM-IV criteria and was tested for content validity by administration of the interview in 323 persons with a claim for disability benefit (Cornelius et al., 2014). The content validity of the DIAD was considered moderate to good by expert agreement. Thereafter, the DIAD has not been validated or administered in studies investigating AD in patients with cancer. During that same time period, a

module to diagnose AD was developed (Perkonigg et al., 2015) and was incorporated into the Diagnostic Expert System for mental disorders/Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI, later updated to DIA-X-5) (Wittchen & Pfister, 1997). This system is used to assess MDs according to DSM-5 and ICD-11 criteria. Although not verified for the field of oncology, the AD module was found to be a reliable, valid assessment of the ICD-11 diagnosis (Perkonigg et al., 2021), but the rationale and design of this module has not yet been published. A year later, in 2016, the Dutch guideline 'Adjustment Disorder in patients with cancer' (TrimbosInstitute, 2016) was published also including a diagnostic interview for AD. This was the interview that we used in the studies in **Chapters 4** and **5**. There are some similarities and differences between the content of the guideline-based interview and the other diagnostic interviews. When taking a closer look at the content analysis in **Chapter 5**, it is demonstrated that the pillars can be divided into (1) physical, psychological and social themes in the pillar Stressors; (2) physical, autonomy, spiritual/existential and social themes in the pillar Resilience; and (3) physical, psychological and social themes in the pillar Symptoms and Complaints. Each theme is subdivided in specific subthemes with accompanying topics. When comparing these subthemes and topics with the DIAD, similar symptoms of AD are listed (symptoms of worrying, restlessness, over-emotionality, and the impact of symptoms on functioning). Additionally, specific symptoms like worry, recurrent and distressing thoughts about the stressor, rumination, and the process of adaptation after cancer diagnosis show major resemblances with listed items in the AD module of the DIA-X-5. Apparently, regardless of the choice of interview or applied AD definition, the same information regarding Stressors and Symptoms is retrieved. The topic resilience is the largest discriminating factor in the three diagnostic interviews. Resilience is commonly described as 'the ability to bounce back' or 'positive responses or outcomes in the face of significant risk or adversity' (Vella & Pai, 2019). Resilience and its related themes (for example sense of control, emotional support, purpose in life and meaning) appear to be important for establishing an AD diagnosis in the guideline-based interview for patients with cancer and are not explicitly stated in the ICD-11 or DSM-5. For example, the ICD-11 criterium *failure to adapt* (Criterium 3) is negatively formulated compared to subtheme *adaptive distraction seeking* as mentioned in the guideline-based interview. The focus on negative aspects regarding the psychological response to cancer is also reflected in the adherence to the interview manual, where interviewers asked questions regarding Stressors and Symptoms and Complaints more thoroughly compared to those about Resilience. The tendency of focussing on negative aspects can be explained by the outline of a structured clinical interview, where the focus lies on the absence of a (combination of) symptoms resulting in *no mental disorder diagnosis* and the presence of a (combination of) symptoms results

into a *mental disorder diagnosis*. Meanwhile, it has been demonstrated that focussing on resilience can clarify the coping response (Deshields et al., 2016) or positive states (Aspinwall & MacNamara, 2005) that people show, when facing a challenging event. Resilience could therefore predict a potential successful recovery from increased psychological symptoms. Adding resilience as a topic of interest when diagnosing AD, could provide the opportunity for discriminating a normal adaptive response from a maladaptive response or mental disorder.

The three independent initiatives to develop a diagnostic interview for AD from several research groups suggests that the accessibility and successful implementation of a valid AD diagnostic instrument in research and clinical practice is limited. As now three diagnostic interviews for AD are available, future studies could focus on which diagnostic interview is the most accurate in diagnosing AD, or which interview is the most suitable to administer in patients with cancer, or both. This is in line with the call from Morgan and colleagues who highlight the importance of resolving basic scientific questions regarding amongst others diagnostic clarity and assessment measures for AD (Morgan et al., 2022). Diagnostic uniformity concerning the AD diagnosis is important for an accurate interpretation of AD prevalence rates in cancer survivors.

Factors related to (symptoms of) AD

On a cross-sectional level, the diversity of results on associated factors with AD after cancer is large. While our findings in **Chapter 4** show that being employed, diagnosed with cancer less than five years ago, or willingness to talk to a psychologist or social worker are related to higher odds of an AD diagnosis, other studies report that associated factors were not only related to AD but also major depression (Kugaya et al., 2000) and factors were assumed to have a statistical but no clinical effect on the odds of having AD (Hund et al., 2016). Furthermore, the reasoning for investigating specific factors in studies is based on a clinical rationale, for example AD related to smoking in head and neck cancer (Kugaya et al., 2000), or testing a specific hypothesis like AD related to living in rural areas vs. urban areas and physical activity in breast cancer (H. Y. Tang et al., 2020). Stating that specific factors are associated with AD is therefore not yet possible. We would even suggest that observing factors related to trajectories of adjustment would probably be more relevant to describe the patient who reacts resiliently to his or her situation during or after cancer treatment, or the patient who might benefit from psychosocial support.

The investigation of associated factors with symptoms of AD specifically is challenging. In our studies in **Chapter 2** and **Chapter 3** the number of observed cases

meeting the criteria for time-limited or persistent symptoms of AD was too small to perform valid statistical analyses. Other studies investigating associated factors with (symptoms of) AD over time in oncological patient populations also had problems with a small number of observed AD cases, specifically matching the operationalised AD variable in their study. For example, the longitudinal study by Akechi and colleagues (Akechi et al., 2001) merged AD cases with all MDs and defined this as psychological distress. They found that in 129 patients with lung cancer a younger age and the presence of pain were associated with psychological distress at baseline, and higher HADS-scores at baseline were associated with psychologic distress at 6-months follow-up. No associated factors were analysed for patients with AD on both baseline and follow-up. Another study by Akechi and colleagues (Akechi et al., 2004) found that a lower performance status, greater concern about being a burden to others, and less satisfaction with support were factors associated with AD and/or MD in 209 terminally ill cancer patients during their first outpatient visit. Here, again, AD-specific results were not reported. Lastly, Blazquez and colleagues investigated the presence of anxiety, depression, AD, and suicide ideation longitudinally in 103 patients with cancer. They found that women were more likely to suffer from at least one MD compared to men at any time during the study, and that being younger was associated with having at least one MD one week after finishing radiotherapy (Blazquez & Cruzado, 2016). Summarizing, the small sample sizes and diversity in study designs (AD measurement method, time points, and included demographic, clinical, and psychosocial variables) limits the identification of associated factors with AD after cancer over time. This is in line with the findings of a recent systematic review on associated factors with AD, in other patient populations than oncology (Kelber et al., 2022), although the need for more evidence on independent predictors for and associated factors with AD still exists (Kelber et al., 2022; Morgan et al., 2022).

Considerations and future research

Over the years, many clinicians and researchers debated the way the AD diagnosis is defined (Baumeister & Kufner, 2009; Casey et al., 2001; Maercker et al., 2007), and the AD definition and its diagnostic criteria vary for DSM-5 and ICD-11 in the description of symptoms of AD and its course. It is remarkable that experts involved in the DSM and ICD do not have similar ideas on what AD exactly is. One could therefore debate whether the psychological symptoms, impaired functioning in daily life and inability to adjust to a new situation should be captured in another framework, outside of the framework of psychiatric disorders. Instead of a mental disorder, shifting towards considering AD as an emotional and/or behavioural phenomenon, ranging on a continuum might provide chances for formulating and investigating the construct

and precipitating factors of adjustment problems during and after cancer treatment. Two different perspectives on AD are elaborated on.

Abnormal or normal psychological response

The DSM-5 describes how the response to an adverse event should be seen in the light of an AD: "*When bad things happen, most people get upset. This is not an adjustment disorder. The diagnosis should only be made when the magnitude of the distress (e.g., alterations in mood, anxiety, or conduct) exceeds what would normally be expected (which may vary in different cultures) or when the adverse event precipitates functional impairment" (American Psychiatric Association, 2013)*. The review by Carta et al. states that stressful life events, even if brief, may lead to psychopathological alterations (Carta et al., 2009). Contrary to this view, a recent systematic review by Bai et al. states that transient distress symptoms after a cancer diagnosis should be considered normal, and only impaired quality of life should be addressed (Bai, 2022). And, based on the findings in this thesis, it could be stated that only a small percentage of the cancer survivors show persistent psychological symptoms, indicating a MD, and that showing increased psychological symptoms at some point in time during or after cancer treatment is quite common.

These stances raise a general question: what is considered an abnormal response, in terms of increased psychological symptoms? Can individual variations in responses be considered normal, even if the norm for a specific society or culture is different? Who determines whether emotions or behaviour are abnormal, the person experiencing the distress or impairments, significant others surrounding the person or health care professionals? And could the binary view in medical science (the presence or absence of a disease) be considered differently than the psychological response to that disease? The choice of the DSM for including normal expectancies and no 'hard' criteria to define an AD diagnosis is complicated and may lead to differences between the findings of health care professionals. From an ethical point of view, one could also debate whether it is helpful for cancer survivors not adjusting successfully, that their emotions or behaviour are labelled as a mental disease; dealing with a mental disease besides cancer could be interpreted as twice as complicated. And, from a practical point of view, the requirement of having a mental disorder diagnosis before receiving reimbursed psychological treatment contributes to a system of evaluating psychological problems in terms of a disease, instead of considering psychological problems on a continuum ranging from mild to severe and in need of easily accessible support, or specialised support. This thesis does not provide answers to these questions and considerations but does stress that

the concept of an AD diagnosis after a life-event like a cancer diagnosis should be re-evaluated.

Distress or adaptive/maladaptive emotions

Distress as a symptom of AD is described by the DSM (explicitly) and the ICD (optional) and is common in patients with cancer (Mehnert et al., 2018). An impressive number of studies on distress has been performed in various disease phases after a cancer diagnosis and in various tumour type samples. It is believed that increased distress labelled as AD can distinguish those patients not requiring treatment from those who would benefit from specific psychological or pharmaceutical interventions (Maercker et al., 2007). On the other hand, some believe that the labelling of AD in existing classifications reinforces the medicalisation of distress (Bachem & Casey, 2018). And, when taking our studies into account, the possibility of distress decreasing and increasing over time would advocate for watchful waiting with the involvement of healthcare professionals, without interfering the adaptation process of the cancer survivor.

Over the past two decades, the reaction to life events is proposed in another framework, namely the facilitation of emotions in adapting to life events (Tooby & Cosmides, 2008). Recently, a new model by Dekker and colleagues concerning responses to cancer was proposed: an emotional response is adaptive when helping to adapt to events in the environment, and an emotional response is maladaptive when being disproportionally severe or persistent, and interfering with functioning (Dekker et al., 2020). An example of a maladaptive emotion is severe anxiety leading to the avoidance of cancer treatment. This means that the intensity of an emotion alone does not reflect whether this emotion helps to adapt to living with and beyond cancer. The cognitive and behavioural components should be considered as well. A strong emotional experience in response to cancer could be potentially adaptive. The plea is to consider the nature of adaptive and maladaptive emotions in order to detect those patients in need of support (Dekker et al., 2020). This could advocate for clinicians involved in cancer care to distinguish between adaptive emotions and maladaptive emotions, facilitated by the use of screening questionnaires, for optimal case finding of patients in need for emotional support from significant others or peers, or from mental health care.

Limitations and implications

Two important topics must be considered regarding the interpretation of the findings in this thesis concerning the screening for and diagnosing of AD after cancer. First, we made use of the Dutch guideline *Adjustment Disorder in patients*

with cancer to design our studies resulting in the use of the HADS and diagnostic interview to measure symptoms of AD and the diagnosis AD. We are not aware of the use and implementation of the guideline *Adjustment Disorder in patients with cancer* within hospitals or the Dutch mental health care system. Moreover the guideline would require an update for future use given the new developments regarding diagnostic instruments for AD. Second, the studies in this thesis have been designed and written before, during and after the COVID-19 pandemic. The presented data in **Chapter 2** and **3** were previously collected, but the data collection of **Chapter 4** and **5** started in January 2019. After March 2020 (start of COVID lockdown in the Netherlands), data collection continued, but we decided not to include these data for analysis in the planned studies. At that time, we could not predict the impact of possible psychological effects of the COVID-19 pandemic on the participants and on the results of our studies. Neither could we predict how the adjustment in work activities for participating psychologists performing the interviews would influence the diagnostic process, like working online instead of face-to-face and having more time to participate with study patients due to cancellations of regular consultations. Nowadays, more studies have been published investigating AD after the COVID-19 pandemic (where the pandemic is considered the stressor involved in AD) (Taylor, 2021), and for the further exploration of the manifestation of AD after cancer and the experience of the pandemic by people might provide valuable information on how people in general and patients or cancer survivors adjust to a single or multiple major life events.

As demonstrated by this general discussion, there are many questions remaining regarding the manifestation of adjustment problems after a cancer diagnosis. Future studies addressing and possibly resolving these questions, could provide more insight in the psychological symptoms, the impact of these symptoms on daily functioning and the necessity for support for these symptoms and impact. Clarifying these topics could result in patients-centred care, where watchful waiting, self-management, stepped-care including psychological treatment are considered, avoiding overtreatment and reducing healthcare costs.

Taking into consideration that an intense psychological response to cancer is not necessarily a mental disorder, and that (2) balanced attention for the negative and positive consequences of cancer that people experience (physically, psychologically and socially), a first step could be to provide the needed support to facilitate healing, whether it is from significant others, peers, professionals or society.

To conclude, this thesis investigated symptoms of AD and an AD diagnosis in cancer survivors, and debates whether the AD definition is in accordance with daily clinical practice. It is evident that persons react with strong emotions and/or behaviour to such an event, but it is questioned whether an intense emotional or behavioural reaction to a major life-event like a cancer diagnosis or its follow-up should be considered a mental disorder.

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Chapter 7

Summary of the thesis
Samenvatting in het Nederlands

Summary

The overall aim of this thesis is to obtain insight into the presence and course of symptoms of Adjustment Disorder (AD), the prevalence of AD and themes relevant to diagnose AD in patients with cancer and cancer survivors.

Chapter 1 comprises a general introduction to AD after cancer. AD is characterised by an identifiable psychosocial stressor(s), distress and/or significant impairment in social, occupational, or other areas of functioning, and after removal of the stressor(s) the symptoms of AD diminish within six months. The available evidence on AD after cancer is limited in terms of what the prevalence of AD after cancer is, what characterises AD and whether AD is time-limited or persistent in the case of repetitive stressors as in cancer treatment and follow-up. Knowledge on the manifestation of AD after cancer is important for health care professionals to recognise those patients in need for psychological treatment as well as giving directions for future research.

Chapter 2 describes a longitudinal study investigating the course of symptoms of AD in breast cancer survivors (BCS) over one year. The Hospital Anxiety and Depression scale (HADS) was used as an indicator for symptoms of AD, categorised with cut-off scores of HADS-T as indication for no symptoms of a mental disorder (MD) (HADS-T≤10), symptoms of AD (HADS-T 11-14) and symptoms of any other MD (HADS-T≥15). Symptom trajectories were identified based on cut-off scores for 293 BCS with complete data and latent class growth analysis for 459 BCS. Both analyses found that the majority of BCS showed no symptoms of a mental disorder (MD) over time, and that a significant proportion of BCS showed fluctuating symptoms of AD over time. A younger age, less able to handle daily activities, showing more social support discrepancy, neuroticism and less optimism were associated with fluctuating symptoms of AD or any other MD. Assessing symptoms of AD over time is important as symptoms can fluctuate up till five years post-diagnosis.

In **Chapter 3**, the course of symptoms of AD was investigated in patients with colorectal cancer during one year. Here, the proportion of patients with time-limited and persistent symptoms of AD were investigated directly after cancer diagnosis up to one year follow-up. Symptom trajectories were identified based on HADS cut-off scores as described in Chapter 2. In total 194 patients completed the baseline questionnaires, and for 81 patients complete data was available. Where a significant proportion of patients showed no symptoms of an MD (38%) and few patients showed time-limited (9%) or persistent (1%) symptoms of AD, almost half (47%) showed fluctuating symptoms. Higher fear of cancer recurrence, lower

health related quality of life, and higher cancer-specific distress was associated with fluctuating symptoms and symptoms of AD. As the majority of patients showed elevated symptoms of AD at one point in time, it is important to investigate how these elevated symptoms relate to an AD diagnosis.

In **Chapter 4**, the prevalence of AD was investigated in patients with breast, prostate and head and neck cancer, as well as the acceptance of psychological treatment for AD. In this observational study, 200 patients gave informed consent for study participation, and 74 patients participated in the guideline-based semi-structured interview for AD based on elevated scores on the HADS (≥11), Distress Thermometer (≥4) or specific items on the problem list. The overall prevalence of AD was estimated at 13%, and AD was associated with being employed and having a shorter time since diagnosis. The acceptance of psychological treatment was estimated at 65%.

The diagnostic accuracy of the guideline-based semi-structured interview for AD used in Chapter 4 was investigated in **Chapter 5**, by evaluating psychologists' adherence to the manual, interrater agreement on an AD diagnosis and the content of the interview. The interview contains topics on Stressors, Resilience and Symptoms and complaints, providing guidance for interviewers. Nine psychologists performed interviews in patients with cancer resulting in 73 audiotaped interviews. The adherence to the manual was calculated based on the scoring of the manuals' topics by two researchers independently. The interrater agreement was determined by the agreement on an AD diagnosis of the interviewer and an independent assessor. The content of the interview was analysed using thematic analysis. Results showed that the adherence to the interview manual was at least briefly covered for 97% of the topics, and at least adequately for 78% . Stressors and Symptoms were addressed more thoroughly than Resilience. The interrater agreement for the AD diagnosis was moderate (0.55). Topics regarding Stressors and Resilience can be additionally specified into physical, psychological, spiritual, and social themes. This specification is important to perform a balanced investigation of stressors, resilience, and symptoms in patients with cancer to improve the clinical decision-making regarding AD.

Finally, **Chapter 6** is a general discussion of the main findings of the studies included in this thesis. AD appears to be only present in a small percentage of the patients who have (had) cancer. Moreover, fluctuations in psychological symptoms over time is common, so repetitive assessment over time is warranted. Topics regarding stressors, resilience and symptoms are important for a balanced investigation of the context of a patient with cancer and adjustment difficulties. Due to discrepancies between the AD definition and the findings of the studies, this discussion explores

alternative views to describe adjustment difficulties after a cancer diagnosis and treatment outside of the mental disorder framework. The strengths and limitations of the presented work are discussed, and suggestions for future research are given.

Samenvatting

Het doel van dit proefschrift is om inzicht te krijgen in de aanwezigheid en het beloop van symptomen van Aanpassingsstoornis (AS), de prevalentie van AS en relevante thema's voor de diagnose van AS bij patiënten met kanker en mensen die verder leven na de behandeling van kanker (survivors).

Hoofdstuk 1 bevat een algemene inleiding over AS na kanker. AS wordt gekenmerkt door een identificeerbare psychosociale stressor of stressoren, distress en/ of significante beperkingen in sociaal, beroepsmatig of andere gebieden van functioneren. Ook nemen symptomen van AS af binnen zes maanden na het verdwijnen van de stressor(en). Weinig is bekend over de prevalentie van AS na kanker, wat de kenmerken zijn van AS na kanker en of AS tijdelijk of aanhoudend is in het geval van herhaalde stressoren, zoals een kankerdiagnose, -behandeling en follow-up. Kennis over de manifestatie van AS na kanker is belangrijk voor zowel zorgverleners om patiënten te herkennen die psychologische behandeling nodig hebben als om richting te geven voor toekomstig onderzoek.

Hoofdstuk 2 beschrijft een longitudinale studie naar het beloop van symptomen van AS bij borstkanker survivors gedurende een jaar. De Hospital Anxiety and Depression Scale (HADS) werd gebruikt als indicator voor symptomen van AS. Trajecten van symptomen werden geïdentificeerd op basis van HADS-scores van 293 survivors met complete data en op basis van statistische analyses bij 459 survivors (latent class growth analysis (LCGA)). Beide analyses toonden aan dat de meerderheid van de survivors in de loop van de tijd geen symptomen van een psychiatrische stoornis vertoonde, en dat een aanzienlijk deel van de survivors in een langere periode wisselende symptomen van AS vertoonde. Een jongere leeftijd, minder in staat om dagelijkse activiteiten uit te voeren, meer discrepantie tussen ervaren en ontvangen sociale steun, meer neuroticisme en minder optimisme waren geassocieerd met de groep die wisselende symptomen van AS en symptomen van een andere psychiatrische stoornis representeerde. Het is belangrijk om symptomen van AS in de loop van de tijd te observeren, aangezien symptomen van AS tot vijf jaar na kankerdiagnose kunnen voorkomen.

In **Hoofdstuk 3** werd het beloop van symptomen van AS onderzocht bij patiënten met dikkedarmkanker gedurende een jaar. In dit onderzoek werd de verhouding van patiënten met tijdelijke of aanhoudende symptomen van AS bestudeerd, direct na de kankerdiagnose tot een jaar daarna. Trajecten van symptomen werden geïdentificeerd op basis van HADS-scores, op vergelijkbare wijze als in Hoofdstuk 2.

In totaal vulden 194 patiënten na diagnose de vragenlijst in, en voor 81 patiënten waren data van alle vervolgmetingen beschikbaar. Waar een aanzienlijk deel van de patiënten over tijd geen symptomen van een psychiatrische stoornis lieten zien (38%) en slechts enkelen tijdelijke symptomen van AS (9%) of aanhoudende symptomen van AS (1%), vertoonde bijna de helft (47%) wisselende symptomen over tijd. Hogere angst voor terugkeer van kanker, lagere kwaliteit van leven en hogere aan kanker gerelateerde distress werden geassocieerd met wisselende psychiatrische symptomen en symptomen van AS. Aangezien de meerderheid van de patiënten op enig moment verhoogde symptomen van AS vertoonde, is het belangrijk om te onderzoeken hoe deze verhoogde symptomen zich verhouden tot een AS diagnose.

In **Hoofdstuk 4** werd de prevalentie van AS onderzocht bij patiënten met borst-, prostaat- en hoofd- halskanker, evenals de acceptatie van psychologische behandeling voor AS. In deze observationele studie gaven 200 patiënten toestemming voor deelname aan het onderzoek; 74 patiënten namen deel aan het op een richtlijn gebaseerde semi-gestructureerde interview voor AS op basis van verhoogde scores op de HADS (≥11), Lastmeter (≥4) of specifieke items op de probleemlijst. De prevalentie van AS werd geschat op 13%, en AS was geassocieerd met het hebben van werk en een kortere tijd sinds kankerdiagnose. De acceptatie van psychologische behandeling werd geschat op 65%.

De diagnostische nauwkeurigheid van het semi-gestructureerde interview voor AS, dat werd gebruikt in Hoofdstuk 4, werd onderzocht in **Hoofdstuk 5.** Het interview bevat onderwerpen over Stressoren, Veerkracht en Symptomen en klachten, waardoor het handvatten biedt aan interviewers.

In dit onderzoek werd de naleving van de handleiding door psychologen bestudeerd, de betrouwbaarheid van het interview om een diagnose AS te stellen bepaald en de inhoud van het interview geëvalueerd. Negen psychologen voerden interviews uit bij patiënten met kanker, resulterend in 73 opgenomen gesprekken. De naleving van de handleiding werd berekend op basis van het scoren van de onderwerpen in de handleiding door twee onafhankelijke onderzoekers. De betrouwbaarheid van het interview werd bepaald op basis van de overeenstemming over een diagnose van AS tussen de interviewer en een onafhankelijke beoordelaar. De inhoud van het interview werd geanalyseerd met behulp van thematische analyse. De resultaten toonden aan dat de naleving van de handleiding voor ten minste 97% van de onderwerpen kort werd besproken, en voor minstens 78% adequaat werd besproken. Stressoren en symptomen werden grondiger besproken dan veerkracht. De betrouwbaarheid van het interview voor de diagnose AS was

matig (0.55). Onderwerpen met betrekking tot stressoren en veerkracht kunnen verder worden gespecificeerd in fysieke, psychologische, spirituele en sociale thema's. Deze specificatie van de thema's is belangrijk voor het gebalanceerd uitvragen van stressoren, veerkracht en symptomen bij patiënten met kanker om hiermee de klinische besluitvorming rondom AS te verbeteren.

Tot slot, **Hoofdstuk 6** is een algemene bespreking van de belangrijkste bevindingen van de studies in dit proefschrift. AS lijkt slechts bij een klein percentage van patiënten met kanker en survivors aanwezig te zijn. Bovendien zijn schommelingen in psychiatrische symptomen in de loop van de tijd gebruikelijk, dus herhaaldelijke observaties in de loop van de tijd worden aanbevolen. Het uitvragen van stressoren, veerkracht en symptomen zijn belangrijk voor een evenwichtige benadering van de context van patiënten met kanker en survivors met aanpassingsmoeilijkheden. Vanwege verschillen tussen de definitie van AS en de bevindingen van de studies, worden in deze algemene discussie alternatieven verkend om aanpassingsmoeilijkheden na een kankerdiagnose en -behandeling te beschrijven buiten het kader van een psychiatrische stoornis. De sterke en zwakke punten van het gepresenteerde werk en suggesties voor toekomstig onderzoek worden besproken.

Appendix

Research Data Management
Curriculum Vitae
List of Publications
Portfolio
Dankwoord

Research Data Management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants and existing data from published papers. The studies described in chapter 2, 3, 4 and 5 were explicitly excluded from the Medical Research Involving Human Subjects Act (WMO) and were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The medical ethical review committee of the VU University Medical Center has given approval to conduct the study in Chapter 4 (file number IRB00002991). Informed consent was obtained from research participants in Chapter 4, and for Chapter 2, 3 and 5 data was used from participants who did not object to the reuse of their data for research. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage).

Data collection and storage

Data for Chapter 2 and 3 was collected through (electronic) health records and paper-and-pencil (hardcopy). Data for Chapter 4 and 5 were collected through paper (hardcopy), the Netherlands Cancer Registry (NCR), PROFILES (secured online questionnaire program) and audiotaping. Pseudonymized digital data were stored and analysed in the Azure DRE (DRE Portal) and on the department server. Pseudonymized hardcopy data is stored in cabinets on the department. Data were converged from EPIC, PROFILES, NCR or hardcopy to SPSS (SPSS Inc., Chicago, Illinois, USA). Data is only accessible by project members working at the Radboudumc.

Availability of data

All studies are published open access. The data will be archived for 15 years after termination of the study. Reusing the data for future research is only possible after a renewed permission by the participants. The anonymous datasets that were used for analysis are available from the corresponding author upon reasonable request.

Curriculum Vitae

Lonneke Wijnhoven was born on the 24th of April in 1989 in St. Anthonis, the Netherlands. After completing secondary education at the Elzendaalcollege in Boxmeer, 2005, she studied Physiotherapy at the Hogeschool Arnhem en Nijmegen, in Nijmegen, and finished her internship in both Nijmegen and Zürich, Switzerland. In 2010, she studied Biomedical Sciences by first a 'schakeljaar' and continuing with the master Clinical Human Movement Sciences. She wrote her master thesis about pain processing, movement and brain activity in patients with persistent low back pain at the department of Anaesthesiology, Pain and Palliative Care by supervision of dr. Oliver Wilder Smith. From 2013 till 2016, she worked as a physiotherapist in several physiotherapy practices and a rehabilitation centre for patients with persistent pain, fatigue and physical uncertainty. Following her interests regarding culture, music and entrepreneurship, she also worked as a management assistant and HR-manager of theatre de Weijer, Boxmeer. In 2018, she started a PhD trajectory on the diagnosis and course of the Adjustment Disorder at the department of Medical Psychology of the Radboudumc. In 2021, she started her private practice for people with persistent pain and fatigue as a psychosomatic therapist, while continuing working on het PhD trajectory. Her ambition is to deliver excellent clinical care, while contributing to science and education on the topic of physical and mental wellbeing of people experiencing a medical illness.

List of publications

Wijnhoven, L. M. A., Custers, J. A., Kwakkenbos, L., & Prins, J. B. (2022). Trajectories of adjustment disorder symptoms in post-treatment breast cancer survivors. Supportive Care in Cancer, 30(4), 3521-3530.

Van Beek, F. E., **Wijnhoven, L. M. A.**, Holtmaat, K., Custers, J. A., Prins, J. B., Verdonck-de Leeuw, I. M., & Jansen, F. (2021). Psychological problems among cancer patients in relation to healthcare and societal costs: A systematic review. Psycho-Oncology, 30(11), 1801-1835.

Van Beek, F. E., **Wijnhoven, L. M. A.,** Custers, J. A. E., Holtmaat, K., De Rooij, B. H., Horevoorts, N. J. E., ... & Jansen, F. (2021). Adjustment disorder in cancer patients after treatment: prevalence and acceptance of psychological treatment. Supportive Care in Cancer, 1-10.

Van Beek, F. E., **Wijnhoven, L. M. A.,** Jansen, F., Custers, J. A., Aukema, E. J., Coupé, V. M., ... & Verdonck-de Leeuw, I. M. (2019). 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. BMC Psychology, 7, 1-11.

Wijnhoven, L. M. A., Kwakkenbos, L., Verdonck-de Leeuw, I. M., Prins, J. B., & Custers, J. A. E. (2023). Evaluating time-limited and persistent symptoms of adjustment disorder in cancer patients after a colorectal cancer diagnosis: a longitudinal observational study. Journal of Psychosocial Oncology Research and Practice, 5(3), 00.

Wijnhoven, L. M. A., van Zutphen, L., Custers, J. A., van Beek, F. E., Holtmaat, K., Jansen, F., ... & Prins, J. B. (2024). Diagnosing adjustment disorder in patients with cancer: evaluation of the adherence, interrater agreement, and content of a guideline-based interview. Journal of Psychosocial Oncology Research and Practice, 6(1), 00.

PhD portfolio of Lonneke Wijnhoven

Department: Medical Psychology
PhD period: 01/12/2018 – 01/10/2023
PhD Supervisor(s): Prof. J.B. Prins, prof. I.M. Verdonck-de Leeuw
PhD Co-supervisor(s): Dr J.A.E. Custers, dr F. Jansen

Training activities	Hours
Courses	
• RIHS - Introduction course for PhD candidates (2019)	15.00
• How to write a medical scientific paper (2019)	4.00
• RU - Scientific Writing for PhD candidates (2019)	84.00
• Radboudumc - eBROK course (2019)	42.00
• RU - Projectmanagement for PhD candidates (2019)	52.00
• RU - Design and Illustration (2020)	26.00
• Radboudumc - Scientific integrity (2021)	20.00
• Workshop Negotiation Skills (2022)	1.00
• Prepare your defence (2022)	1.50
Seminars	
• Radboudumc Medical Psychology Research Seminar (2019)	5.00
• Theme Women's Cancers participation (2019)	3.50
• Early Career Research Network (2019)	5.00
• Webinar Publishing Open Access (2020)	1.75
• Seminar Scientific Integrity (2021)	1.50
• Early Career Research Network (2021)	4.00
• Webinar Scientific Integrity (2021)	1.50
Conferences	
• Congres Nederlandse Vereniging voor Psychosociale Oncologie (2019)	8.00
• Conferentie Onderwijs en Onderzoek (2019)	1.50
• PhD Retreat (2019)	16.00
• CaRe Symposium (2020)	4.00
• Congres Nederlandse Vereniging voor Psychosociale Oncologie (2020)	8.00
• Posterprestentatie NVPO congres (2020)	
• International Congress of Behavioral Medicine - online (2021)	16.00
• Posterpresentatie ICBM (2021)	
• PhD Retreat (2022)	16.00
• Oral presentation PhD Retreat (2022)	
Other	
• Radboudumc - General Radboudumc introduction for research personnel (2017)	9.00
• Journal Club Medische Psychologie (2020)	7.00
• PhD-council member & peer intervision organisation (2020)	60.00
• Gamma Council member and secretary (2021)	25.00
• Algemeen OnderzoekersOverleg MPS (2021)	25.00
• Afdelingsoverleg Medische Psychologie (2021)	6.00
Teaching activities	
Supervision of internships / other	
Coach (Bio)medical bachelor students (2019)	7.00
Meet the PhD (2021)	8.00
Total	**484.25**

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A

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