Chapter 1

General introduction
Cancer-related fatigue: The scale of the problem

A growing group of individuals is affected by cancer and its long-term adverse outcomes. Due to the aging population, widely available screening programs, and advanced treatment options, an increasing number of individuals is expected to be diagnosed with and to live past their cancer diagnosis (Siegel et al., 2012). In the Netherlands, the 5-year cancer survival rate has improved from 41% to 54% for men and from 57% to 63% for women between 1989 and 2007 and is predicted to increase further in the upcoming years. It is expected that 660,000 individuals will be living with a cancer diagnosis in 2020, a substantial increase compared to the prevalence rate of 419,293 documented in 2009 (KWF Kankerbestrijding, 2011). Similar trends are expected in the United States where the number of individuals living with a past cancer diagnosis is estimated to rise from 13.7 million in 2012 to almost 18 million in 2022 (Siegel et al., 2012). Colorectal cancer is among the most prevalent cancer types in both men and women (KWF Kankerbestrijding, 2011; Siegel et al., 2012). In the Netherlands, more than half of the patients with colorectal cancer can expect to be alive 5 years after receiving their diagnosis (i.e., 5-year relative survival rate of 59% for men and women; KWF Kankerbestrijding, 2011). Due to the high prevalence and relatively high survival rate, colorectal cancer patients can be expected to form a substantial proportion of the individuals living past a cancer diagnosis.

The expected increase of individuals living with a history of cancer stresses the pressing need to address the patients’ long-term adverse outcomes. One of the most common and interfering symptoms cancer survivors (see Box 1) experience is cancer-related fatigue (Arndt, Stegmaier, Ziegler, & Brenner, 2006; Jones et al., 2016; Thong et al., 2013). The National Comprehensive Cancer Network [NCCN] defines cancer-related fatigue as “distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (NCCN, 2016). This definition stresses the multidimensional character of cancer-related fatigue that is experienced on a physical, emotional and cognitive level.
General introduction

Box 1: Cancer survivor
In the current thesis, the term cancer survivor is used to broadly refer to cancer patients who have completed their cancer treatment or those who live beyond their cancer diagnosis without being treated with curative intent. The term survivor has been subject to debate as it might elicit associations of a cancer diagnosis with a battle. By no means is the use of this term intended to align with this association or offend people diagnosed with cancer and their close ones.

Cancer-related fatigue from an intrapersonal perspective
In order to understand the scope of the fatigue problem, it is necessary to investigate the prevalence and development of fatigue as well as its adverse effects on patients’ daily life (i.e., fatigue interference, goal disturbance). Further, more research is needed that investigates factors that explain fatigue in patients after the completion of their cancer treatment. Insights into the development of fatigue and predictors of post-treatment fatigue are prerequisites to establish interventions aiming to relieve the fatigue burden in the growing group of patients living with a past cancer diagnosis.

Development and interfering effects of cancer-related fatigue
There is ample evidence that fatigue is experienced by the majority of cancer patients during their cancer treatment (Prue, Rankin, Allen, Gracey, & Cramp, 2006; Servaes, Verhagen, & Bleijenberg, 2002a) and one quarter to one third of patients who have completed treatment (Jones et al., 2016; Servaes, Gielissen, Verhagen, & Bleijenberg, 2007). These findings stress that cancer-related fatigue is highly common during treatment and implies that some cancer patients recover from fatigue after treatment completion, while some remain fatigued. However, most studies on the prevalence of fatigue have either a cross-sectional design or a longitudinal design reporting on average group-trends in the development of fatigue (e.g., Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2013; Jones et al., 2016). Yet, whether and how fatigue develops differently for subgroups of patients from diagnosis, throughout treatment and until survivorship is still largely unknown. Further, as cross-sectional and longitudinal study designs assess fatigue retrospectively over the course of weeks or months, we lack knowledge on how fatigue develops in shorter time intervals, that is, within several hours within the day.

The burden of fatigue is high. Cancer-related fatigue is associated with a substantial loss of quality of life (Schmidt et al., 2012) and interferences in many
domains ranging from daily and occupational functioning to patients’ social life and mental health (Curt et al., 2000; Donovan, McGinty, & Jacobsen, 2013; Dorland et al., 2016; Meeske et al., 2007). Many patients report fatigue as one of their most interfering symptoms, even more so than pain or nausea (Arndt et al., 2006; Stone et al., 2003), which underlines the burden fatigue puts on the patients. Understanding how fatigue develops over time and how it relates to interferences, both longitudinally and within days, is necessary to formulate recommendations about screening and treatment of patients most likely to be affected by long-term fatigue and its adverse effects.

**A cognitive-behavioral model of cancer-related fatigue**

Since the 1990s, evidence is accumulating that clinical variables, such as cancer diagnosis or treatment modalities, are unrelated to or insufficient to explain persistent long-term fatigue (e.g., Andrykowski, Curran, & Lightner, 1998; Servaes et al., 2002a; Smets et al., 1998). Instead, research suggests that psychosocial variables such as cognitions and behaviors are related to fatigue in the long-term (e.g., Goedendorp et al., 2013; Servaes, Verhagen, & Bleijenberg, 2002b). These findings support a cognitive-behavioral model of fatigue (Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007), which suggests a distinction between precipitating and perpetuating factors of cancer-related fatigue. That is, while clinical variables are assumed to initially precipitate fatigue, mostly cognitive and behavioral variables are expected to perpetuate fatigue after treatment has been completed. Most prominently, catastrophizing cognitions about fatigue (e.g., worrying that the fatigue will become worse) have been shown to predict long-term fatigue in cancer survivors (Goedendorp et al., 2013; Lukkahatai & Saligan, 2013). This finding demonstrated that intrapersonal cognitions might maintain fatigue after treatment completion. Indeed, cognitions appear to be potent targets for interventions aiming to relieve the fatigue burden in cancer survivors. That is, cognitive behavior therapy developed to target maladaptive cognitions (Bleijenberg, Gielissen, Bazelmans, Berends, & Verhagen, 2004) has been shown to be effective in relieving patients’ fatigue burden (Gielissen, Verhagen, & Bleijenberg, 2007; Gielissen, Verhagen, Witjes, & Bleijenberg, 2006). However, much about the perpetuating effect of maladaptive cognitions remains unknown. For example, we currently lack knowledge about which affective (i.e., changes in mood) and
behavioral processes (i.e., changes in activity) explain how catastrophizing unfolds its maladaptive effect on fatigue in daily life. Behavioral perpetuating factors have received relatively little research attention, but negative social interactions and a perceived lack of social support have been shown to contribute to persistent fatigue after treatment completion (Goedendorp et al., 2013; Servaes et al., 2002b). In the cognitive-behavioral tradition, behaviors are mainly considered from the patient-perspective and not as a dynamic interpersonal process limiting our current understanding of which behaviors should be targeted in interventions aiming to relieve post-treatment fatigue.

Cancer-related fatigue from an interpersonal perspective

Another important development since the 1990s is the recognition that coping with a stressor is a dyadic interpersonal process, rather than an isolated intrapersonal endeavor (Bodenmann, 1995, 1997; Coyne & Smith, 1991; DeLongis & O’Brien, 1990). That is, many patients do not cope alone, but experience a stressor such as cancer in the context of their relationship. The concept of dyadic coping emphasizes that both partners of the couple react to and cope with a stressor as an interrelated system (Bodenmann, 2005; Hagedoorn, Sanderman, Bolks, Tuinstra, & Coyne, 2008; Traa, De Vries, Bodenmann, & Den Oudsten, 2015). The coping strategies of cancer patients and their partners can take on various forms (e.g., empathic understanding, protective buffering) and as such can have both adaptive and maladaptive effects on individual and relationship outcomes (Bodenmann, 2005; Regan et al., 2015). Cancer-related fatigue can be conceptualized as a stressor the dyad copes with as an interrelated system. As such, considering the dyadic context can help us understand the interpersonal factors that might perpetuate fatigue, as well as the impact of dyadic coping efforts on the couples’ relationship. Two interpersonal models can be applied.

The operant model applied to cancer-related fatigue

The operant model in the field of pain (Fordyce, 1976) acknowledges that symptoms are not experienced in isolation but within a social context that might contribute to the patient’s symptom development. The model states that partner responses towards patients’ illness-behavior (e.g., resting) and well-behavior (e.g., being active) can either function as reinforcement or punishment. As such, partner responses
can either increase or reduce the frequency of illness-behaviors and hence impact other symptom outcomes, including symptom severity and symptom interferences (i.e., the degree to which patients’ symptoms interfere with their daily life such as work and social activities). Solicitous partner responses, such as taking over household chores, are considered to be maladaptive as they reinforce illness-behavior. Punishing partner responses, such as responding with frustration, are considered to be adaptive as they discourage illness-behavior. Research on pain in the tradition of the operant model provided ample evidence that partner responses have the potential to relieve or worsen patients’ symptom outcomes (e.g., Newton-John, 2002). These studies have been vital, as they demonstrated that symptoms are amenable to social contingencies and that their long-term developments cannot be fully understood without investigating partner behaviors. There is some evidence suggesting that also cancer-related fatigue might be amenable to social interactions (e.g., Goedendorp et al., 2013). However, contrary to the field of pain, we currently lack knowledge on how partner behaviors in couples coping with post-treatment fatigue might impact the patients’ fatigue experience.

The intimacy model applied to cancer-related fatigue
While the operant model acknowledges that symptoms are experienced within a social context, it is limited in mainly conceptualizing partners as exerting influence upon the patients’ symptom experience. However, the dyadic context might not only shape symptom outcomes, but the context itself might get shaped by how couples cope. Put differently, partner behaviors might not only impact the patient’s symptom outcomes, but also the couple’s relationship. Given that a healthy relationship is an important coping resource for both cancer patients and their partners (Drabe, Wittmann, Zwahlen, Büchi, & Jenewein, 2013; Manne & Badr, 2008; Yang & Schuler, 2009), it is crucial to look beyond symptom outcomes and also investigate which partner behaviors are a potential benefit or harm to the couples’ relationship.

The interpersonal process model of intimacy (Reis & Shaver, 1988) provides a framework to investigate partner behaviors’ influence on the couples’ relationship. The model states that the development of intimacy is a dynamic, dyadic process. If one partner’s self-disclosure is met with a response that communicates understanding, validation and caring, intimacy develops. Partner responses that fail to
convey this responsiveness can create distance between partners and thus harm the couples’ relationship satisfaction. Evidence that partner support is associated with an increase in feelings of intimacy in patients diagnosed with cancer (Belcher et al., 2011) supports the rationale of this model. As such, the intimacy model allows conceptualizing partner behaviors as interpersonal processes that can either benefit or harm the couples’ relationship. However, only recently, researchers called attention to the impact of partner behaviors on the relationship in couples coping with pain (Cano & Williams, 2010; Prenevost & Reme, 2017). Hence, the impact of partner behaviors on relationship outcomes in couples coping with interfering and persistent symptoms, including fatigue, is not yet well understood.

Depending on the underlying research tradition, qualitatively different forms of partner behaviors are investigated. While research in the tradition of the operant model focuses on a variety of partner responses, research in the tradition of the intimacy model focuses on partner communications. Other than the unilateral partner responses, partner communications entail mutual and dynamic partner behaviors to which both dyad members contribute. For example, communications characterized by mutual self-disclosure have been associated with positive relationship outcomes while hiding one’s concerns about cancer (i.e., protective buffering) has consistently been associated with negative relationship outcomes (Regan et al., 2015). Currently, we lack insight into communications that are specifically related to the adverse effects of cancer such as fatigue (e.g., co-rumination, couples’ communication extensively focusing on the negative aspects of fatigue) and how these conversations might not only influence the couples’ relationship but also patients’ symptom outcomes. Put differently, partner communications about fatigue might be another behavioral perpetuating factor of fatigue and, at the same time, influence the couples’ relationship. Integrating the operant model and intimacy model provides a valuable framework to investigate several partner behaviors (i.e., partner responses, couples’ communications) and their effects on both, individual patient outcomes as well as relationship outcomes.

A daily life perspective on cancer-related fatigue
Previous research provided important insights into the prevalence of cancer-related fatigue, its potential predictor variables and the relevance of intra- and interpersonal processes in the adjustment to a chronic stressor. However, much research
Chapter 1

shares the limitation that it conceptualizes and measures cognitions, behaviors, symptoms or relationship outcomes as rather static. That is, traditional research designs (e.g., cross-sectional studies) ask participants to provide a summarized report on their psychosocial states across the previous weeks or months. However, psychosocial states and symptoms are dynamic processes that unfold their effects in the context of daily life. Recent research supports this notion and demonstrated that catastrophizing cognitions (Burns et al., 2015; Holtzman & DeLongis, 2007), partner behaviors (Badr, Pasipanodya, & Laurenceau, 2013; Wilson, Martire, & Sliwinski, 2017), cancer-related fatigue (Kober et al., 2016; Timmerman, Dekker-van Weering, Tönis, Hermens, & Vollenbroek-Hutten, 2015) and relationship variables (Belcher et al., 2011; Debrot, Siegler, Klumb, & Schoebi, 2017) vary meaningfully on a daily level. In order to better understand which factors perpetuate fatigue and how dyadic coping impacts fatigue outcomes as well as the couples’ relationship, we need to investigate psychosocial concepts as dynamic processes that occur in the patients’ flow of everyday life.

The diary method (see Box 2) is well suited to investigate dynamic processes as they unfold within individuals in their daily lives. Briefly, the repeated assessments of the diary method capture fluctuations of the concepts of interest and allow investigating their temporal relationships. Second, the (semi-)momentary measures reduce methodological problems of traditional designs (i.e., recall- bias). Third, diary data provide insight into the daily life of the participants as it naturally occurs and unfolds, fostering ecological validity and generalizability of the results obtained (Bolger, Davis, & Rafaeli, 2003; Heron & Smyth, 2010). By this, research questions can be addressed that are different from those investigated with traditional research designs. For example, traditional designs allow investigating whether patients experience more fatigue when they engage in higher levels of catastrophizing as compared with others (between-person differences) while the diary design allows investigating whether patients experience an increase in fatigue when they engage in higher levels of catastrophizing than typical for them (within-person process). As such, research acknowledging the dynamic nature of psychosocial processes and focusing on participants’ daily life has great theoretical and clinical value as it provides insights into daily within-person processes (e.g., increases in catastrophizing) that can be targeted in interventions aiming to relieve fatigue.
Box 2: Diary method
In the current thesis, the term *diary design/method* is used to refer to studies employing an intensive longitudinal design. These designs are known under various names, e.g., ecological momentary assessment [EMA], experience sampling method [ESM], ambulatory assessment or diary study. All of these designs share the feature that time-varying constructs (e.g., cognitions, behaviors) get assessed repeatedly within individuals over time as they occur naturally in the individuals’ daily life (Bolger & Laurenceau, 2013; Schneider & Stone, 2016; Shiffman, Stone, & Hufford, 2008). A dyadic diary design refers to designs in which both members of a dyad, often intimate partners, report on their daily life experiences in the context of their relationship (Laurenceau & Bolger, 2005).

Cancer-related fatigue in a couples’ context: The role of daily cognitions and partner behaviors
The cognitive-behavioral model and the operant model pushed the field of chronic symptom development forward by acknowledging that distinct factors are responsible for the initiation and perpetuation of symptoms and by demonstrating that symptoms are experienced within a social context that can contribute to their development. The intimacy model provides a complementary framework to understand how couples’ behaviors can influence the dyads’ adjustment to cancer and it directs attention explicitly to partner communications as another potential behavioral perpetuating factor of fatigue. Together, these models provide an intrapersonal and interpersonal perspective to study perpetuating factors of fatigue.

The current thesis builds upon these models to investigate how intrapersonal cognitions and interpersonal partner behaviors can impact the patient’s fatigue experience as well as the couple’s relationship satisfaction. In order to gain ecologically valid insights in cognitions and partner behaviors and to understand their fluctuations and within-person effects on daily fatigue and relationship outcomes, a daily perspective is applied. The insights of this thesis are hoped to inform the development and improvement of treatment modules aimed to relieve the symptom burden in couples coping with cancer-related fatigue while preserving the couples’ relationship satisfaction. Based on the outlined models and previous research, the following four questions guided the research presented in this thesis:

1. How do cancer-related fatigue and its interfering effects develop longitudinally and in daily life?
Chapter 1

2. Which intrapersonal cognitions can be targeted to benefit individual and relationship outcomes?
3. Which interpersonal partner behaviors can be targeted to benefit individual and relationship outcomes?
4. What can we learn from the integration of an intrapersonal and interpersonal perspective to study cancer-related fatigue?

Outline of this thesis

By applying an intrapersonal as well as an interpersonal perspective, a dyadic diary design, and advanced statistical analyses, the following studies provide unique insights into perpetuating factors of cancer-related fatigue as well as adaptive and maladaptive dyadic coping processes and their impact on the couple’s relationship, see Table 1.

This thesis starts by demonstrating the relevance of the two central concepts of this thesis, cancer-related fatigue and adjustment to disease in a dyadic context, on a population level. That is, chapter 2 was dedicated to identify and describe subgroups of patients that differ in their longitudinal development of cancer-related fatigue and its associated goal disturbance. In chapter 3, the important role of patients’ relationship status and living arrangement in mitigating the adverse effects of chronic disease has been studied. Together, the findings stress the clinical relevance of the fatigue problem and imply that daily partner behaviors are an important context to study disease outcomes. These two chapters laid the groundwork for the next chapters, which systematically address daily perpetuating factors of patients’ fatigue outcomes and predictors of couples’ relationship satisfaction from an intrapersonal and interpersonal perspective. Based on the three guiding models, two classes of predictor and outcome variables are investigated, see Figure 1. Predictor variables include cognitions (i.e., patients’ and partners’ catastrophizing thoughts about fatigue) and partner behaviors (i.e., partner responses, patients’ and partners’ co-rumination) while the outcomes of interest are patients’ fatigue outcomes (i.e., fatigue severity, fatigue interference) and the couples’ relationship (i.e., patients’ and partners’ relationship satisfaction). By applying a dyadic diary design, these chapters provide insights into how daily cognitions and partner behaviors translate into changes in fatigue outcomes and relationship satisfaction in daily life.
### Table 1

**Overview of the empirical chapters**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Sample</th>
<th>Design</th>
<th>Perspective</th>
<th>Aim</th>
<th>Statistical analysis &amp; software</th>
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<tbody>
<tr>
<td>2</td>
<td>Colorectal cancer patients (n = 183)</td>
<td>Longitudinal, following cancer patients from diagnosis to 18 months later</td>
<td>Intrapersonal</td>
<td>Identify subgroups of patients differing in the severity and development of their fatigue and goal disturbance.</td>
<td>Growth Mixture Modeling: trajectory analyses</td>
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<td>3</td>
<td>Dutch general population (n = 25214)</td>
<td>Cross-sectional, baseline data of the LifeLines cohort study</td>
<td>Interpersonal</td>
<td>Study the mitigating effect of relationship status and living arrangement on the adverse effects of single and multiple morbidity.</td>
<td>Analyses of covariance: moderation model</td>
</tr>
<tr>
<td>4</td>
<td>Colorectal cancer survivors (n = 101)</td>
<td>Daily diary study, repeated measurements within 14 days</td>
<td>Intrapersonal</td>
<td>Investigate the perpetuating role of catastrophizing in daily life and its affective and behavioral mediators.</td>
<td>Multilevel modeling: mediation model</td>
</tr>
<tr>
<td>5</td>
<td>Colorectal cancer survivors and their partners (n = 101)</td>
<td>Dyadic daily diary study, repeated measurements within 14 days</td>
<td>Interpersonal</td>
<td>Analyze the effect of partner responses towards patients’ fatigue- and well-behavior on fatigue interference and relationship satisfaction and the moderating effect of current fatigue severity.</td>
<td>Multilevel modeling: moderation model</td>
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<tr>
<td>6</td>
<td>Colorectal cancer survivors and their partners (n = 101)</td>
<td>Dyadic daily diary study, repeated measurements within 14 days</td>
<td>Intra- &amp; Interpersonal</td>
<td>Investigate the effects of patient and spouse catastrophizing and the dyads co-rumination on patients’ fatigue and couples’ relationship satisfaction.</td>
<td>Multilevel Structural Equation Modeling: actor- and partner-effect analyses incorporating mediation (APIM, APIMeM)</td>
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First, turning to cognitions that might perpetuate cancer-related fatigue after treatment completion, chapter 4 focuses on cancer survivors’ catastrophizing thoughts and their reciprocal relationship with fatigue as well as potential behavioral and affective mediators of this relationship. The last two chapters adopt an interpersonal perspective to increase our insight into dyadic processes that may either relieve or worsen symptom outcomes and might simultaneously impact the couples’ relationship. Chapter 5 aimed to identify daily partner responses towards patients’ fatigue- and well-behavior that might either foster or hamper the patients’ fatigue interference as well as relationship satisfaction. Further, it acknowledges that the severity of fatigue fluctuates within patients across days and as such might modify the impact of partner responses on fatigue and relationship outcomes. Lastly, chapter 6 links the study of cognitions and partner behaviors and assessed their effects on individual patient outcomes as well as both dyad members’ relationship outcomes. Applying a dyadic method of data analyses, it is investigated whether patients’ and partners’ catastrophizing translate via couples’ co-rumination into patients’ fatigue severity while also considering the effect of co-rumination on both partners’ relationship satisfaction.

**Figure 1.** Schematic display of the concepts and associations investigated in Chapter 4 – 6.
References


Chapter 1


Chapter 1


General introduction


