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Unintentional weight loss after head and neck cancer : a dynamic relationship with depressive symptoms

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UNINTENTIONAL WEIGHT LOSS AFTER HEAD AND NECK CANCER: A DYNAMIC RELATIONSHIP WITH DEPRESSIVE SYMPTOMS

by

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CERTIFICATE OF APPROVAL

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ABSTRACT

Although unintentional weight loss (UWL) and depressive symptoms are critical outcomes following diagnosis and treatment for head and neck cancer (HNC), there is a limited understanding of how they influence one another over time. As part of a large, prospective study on HNC outcomes, growth curve modeling was used to evaluate 564 patients' trajectories of depressive symptoms and percentage UWL and analyze longitudinal associations between these variables across the first year following HNC diagnosis. The hypothesized temporal precedence model was not supported—pretreatment depressive symptoms predicted neither total percentage weight loss at 6 months (t (561) = -1.50, p = .13), nor rates of curvilinear change in percentage weight loss over time (t (561) = 1.38, p = .17). The opposite temporal precedence model also lacked support—early weight loss predicted neither level of depressive symptoms at 6 months (t (432) = 0.24, p = .81), nor rates of linear change in depressive symptoms over time (t (432) = 1.31, p = .19). Instead, a pattern of concurrent covariation emerged—*changes* in depressive symptoms *over time* were associated with concurrent changes in UWL (t (1148) = 2.05, p = .041) and *changes* in UWL *over time* were associated with concurrent changes in depressive symptoms (t (556) = 2.43, p = .015). That is, to the extent that depressive symptoms increased on a monthly basis, patients lost incrementally more weight than was lost due to the passage of time, and to the extent that weight loss increased on a monthly basis, depressive symptoms also increased.

Together, these bidirectional results depicted an ongoing transactional interplay between depressive symptoms and UWL across time, such that changes in either variable resulted in deviations from the average trajectory of the other variable. Patient-reported pain and eating abilities emerged as potential mechanisms through which these variables influence one another.

The results have important clinical implications, indicating that ongoing screening and treatment for depression and weight loss throughout the first year after HNC could benefit patients' psychological and nutritional outcomes alike.

PUBLIC ABSTRACT

During the months following diagnosis and treatment for head and neck cancer, patients are at risk for development of depression and nutritional decline. Evidence from other medical populations suggests that depression and nutritional deterioration may influence each other over time, yet little is known about their association in head and neck cancer patients. By measuring 564 patients' depressive symptoms and unintentional weight loss for one year after head and neck cancer diagnosis, this study examined several ways that depression and nutritional deterioration could be associated. It was expected that pretreatment levels of depression would predict subsequent weight loss outcomes, however, this was not found. Likewise, degree of early weight loss did not predict subsequent depression outcomes. Instead, a dynamic, reciprocal association between these variables across time existed—to the extent that either variable increased during the first year after diagnosis, so did the other, beyond the way in which it would have changed simply due to the passage of time since diagnosis. Given that depressive symptoms and weight loss changed in concert across time, interventions that target and improve one of these variables may ultimately also improve the other. It is noteworthy that depressive symptoms were associated with weight loss, given that most other risk factors for nutritional decline in this population are non-modifiable aspects of the disease and its treatment. This study advances our understanding of the longitudinal associations between these important clinical outcomes, which can ultimately improve patients' quality and quantity of life.

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INTRODUCTION TO THE RESEARCH QUESTION

Diagnosis and treatment for head and neck cancer (HNC) are frequently accompanied by physical impairments and psychological distress. Essential functions such as speaking, breathing, and eating may become permanently impaired due to the tumor location and treatment-related sequelae. Given such structural and functional changes in this region of the body, nutritional deterioration is a common experience before, during, and following HNC treatment. Nutritional decline, whose earliest and most readily assessed indicator is unintentional weight loss (UWL), has implications for treatment complications and survival (Datema, Ferrier, & Baatenburg de Jong, 2011; van Bokhorst-de van der Schueren et al., 1997). Moreover, the functionally, attitudinally, and socially impactful treatment-related disfigurement and dysfunction accompanying this diagnosis suggest why HNC has been described as one of the most psychologically distressing cancers to experience (Howren, Christensen, Karnell, & Funk, 2013; Katz, Kopek, Waldron, Devins, & Tomlinson, 2004). In particular, prevalence rates of depression and suicide among HNC patients rate among the highest in comparative analyses across cancer sites (Massie, 2004; Misono, Weiss, Fann, Redman, & Yueh, 2008; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001).

Across diverse medical patient populations, inverse associations between depression and nutritional parameters have been identified. These primarily cross-sectional studies have indicated that depression is associated with greater UWL or other indicators of impaired nutritional status. Despite the importance of nutritional factors and the high prevalence of depression in HNC, relationships between psychological and nutritional factors have received minimal research attention and the longitudinal nature of these associations is poorly understood. Although a meaningful relationship between depression and malnutrition in HNC was suggested

as early as 1988 (Westin et al., 1988), the first prospective analysis was only recently published (Britton et al., 2012). In this recent study, baseline depression was a significant independent predictor of malnutrition following the completion of radiation treatment, which was interpreted as an indication that depression influences the development of malnutrition in HNC patients (Britton et al., 2012). Alternatively, it is plausible that experiencing nutritional deterioration early in the HNC experience could influence subsequent depression, perhaps in response to experiencing such a decline in physical health. Examinations of this hypothesized temporal precedence of weight loss on depression have not been conducted in HNC patients. Moreover, the possibility of a more complex, reciprocal association between these variables has been suggested (Britton et al., 2012), but not examined.

The few existing analyses of associations between depression and indicators of nutritional deterioration in HNC patients failed to account for potentially relevant factors such as presence of eating-related impairments. Additionally, research has been limited to patients treated with radiation therapy, small samples, end points that fail to extend much beyond posttreatment, and regression-based analytic approaches. These factors restrict the current literature's ability to make representative, nuanced, and predictive conclusions regarding patterns and degrees of change across time.

Particularly in this population in which depression is common and nutritional functioning is a critical outcome, an improved understanding of how these constructs influence one other over time is needed. Evidence from other medical patient populations suggests that meaningful relationships may exist. Thus, the overall objective of this dissertation study was to investigate longitudinal relationships between depression and unintentional weight loss within a large cohort of HNC patients, while controlling for relevant disease- and treatment-related factors.

CHAPTER 1: OVERVIEW OF HEAD AND NECK CANCER

The term head and neck cancer is collectively used to describe a group of related tumors, typically squamous cell carcinomas, originating in neighboring locations in the head and neck region. Sites include the oral cavity (e.g., lips, tongue, gums, mouth lining, floor of mouth, and hard palate), pharynx (i.e., throat), larynx (i.e., voice box), paranasal sinuses and nasal cavity, and salivary glands. Tumors originating in the pharynx are further classified into nasopharyngeal (upper-pharynx, i.e., behind the nose), oropharyngeal (mid-pharynx, i.e., soft palate, base of tongue, and tonsils), and hypopharyngeal (lower-pharynx). It was estimated that HNC comprised 3.3% of incident cancer diagnoses in the United States in 2014, with an expected 55,070 new diagnoses and 12,000 deaths (American Cancer Society, 2014). Men are more than two and a half times more likely than women both to be diagnosed with and to die from HNC (American Cancer Society, 2014). Overall HNC incidence rates remained stable in men and decreased by 0.9% in women between 2006 and 2010 (American Cancer Society, 2014). However, oropharyngeal cancer incidence, in particular, has increased as the incidence of tumors associated with human papillomavirus (HPV) infection is escalating. If recent incidence trends continue, the annual number of HPV-related oropharyngeal cancer diagnoses in the United States will soon surpass the annual number of cervical cancer diagnoses, and by 2030 this discrepancy could grow as large as 10,000 cases (Chaturvedi et al., 2011). Although site-specific variation in survival exists (see Cooper et al., 2009), overall HNC survival is approximately 84% at one year, 62% at five years, and 51% at ten years (American Cancer Society, 2014).

Accompanying the site-specific changes in incidence rates are shifting patient demographics and disease outcomes. Patients with HPV-related HNC tend to be younger, wealthier, more educated, more likely to have more lifetime sexual partners (vaginal and oral),

and less likely to have a significant history of tobacco and alcohol use than more traditional HPV-unrelated HNC patients (Joseph & D'Souza, 2012). Despite often being diagnosed at later stages than HPV-unrelated HNC, patients with HPV-related HNC have better three-year survival rates (Chaturvedi et al., 2011; Joseph & D'Souza, 2012). Tobacco and/or excessive alcohol use represent the primary independent and synergistic risk factors for HPV-unrelated HNC. Whereas tobacco use alone increases risk of HNC incidence 5.8 times, co-occurring tobacco and alcohol use is associated with a 19–30 times increased risk of HNC (American Cancer Society, 2014; Stevens, Gardner, Parkin, & Johnson, 1983).

Treatment for HNC can entail surgery, radiation therapy, or chemotherapy, or a combination of these modalities. As a result of the tumor location and treatment effects, many patients experience structural and functional impairments that impact essential daily activities. Many of these physiological changes could contribute to long-term nutritional compromise in HNC patients. Dysphagia (difficulty swallowing) is a chronic concern for up to 69% of patients and has been considered to be the most frequently experienced nutrition-related concern before (Kubrak et al., 2010), during (Larsson, Hedelin, Johansson, & Athlin, 2005), and after HNC treatment (Chasen & Bhargava, 2009). It can result from physiological changes following surgery or from effects of radiation or chemotherapy. Mucositis, characterized by painful inflammation or damage to mucous membranes, occurs in 80% of patients treated with radiation and is associated with hospitalizations and treatment interruptions (Trotti et al., 2003). Patients treated with radiation almost universally experience dysfunction in saliva production resulting in xerostomia (mouth dryness), and/or presence of thick, ropey salivary secretions (Chasen & Bhargava, 2009). Unfortunately xerostomia, which additionally impacts chewing and swallowing abilities, often does not improve following the conclusion of treatment (Couch et al.,

2007; Larsson et al., 2005). Furthermore, patients may experience acute or chronic alterations in taste and smell perception or sensitivity due to chemotherapy drugs and radiation-induced damage (Chasen & Bhargava, 2009).

The reviewed treatment-related sequelae, in addition to loss of teeth and structural changes to the mouth and jaw, can impact patients' abilities to chew, swallow, and taste food in a potentially permanent way. Over half of long-term HNC survivors report problems with eating and 17% continue to experience significant pain five years after diagnosis (Funk, Karnell, & Christensen, 2012). Experiencing such side effects reduces patients' nutritional intake, increases risk of nutritional compromise, and diminishes quality of life (Chasen & Bhargava, 2009; Hammerlid et al., 1998). Furthermore, these impairments may necessitate nutritional interventions, such as individualized dietary counseling, nutritional supplements, appetite stimulant medications, or tube feeding.

CHAPTER 2: DEPRESSION IN HEAD AND NECK CANCER PATIENTS

Prevalence

Compared to other cancer patients, HNC patients report high levels of depressive symptoms. In a sample of 4,496 patients representing 14 cancer sites, HNC patients' average depression scores were the sixth highest (Zabora et al., 2001). Similarly, a comprehensive review of studies assessing depression in cancer patients suggested that the prevalence of depression in oropharyngeal cancer patients is among the highest of all cancer patients (Massie, 2004). When assessed cross-sectionally at a single time point, mild to severe depressive symptomatology has been reported by 15-57% of HNC patients (Archer, Hutchison, & Korszun, 2008; Britton et al., 2012; Duffy et al., 2007; Karnell, Funk, Christensen, Rosenthal, & Magnuson, 2006; Massie, 2004). Although HNC patients report mild to severe depressive symptoms throughout the illness trajectory, the prevalence of these symptoms appears to change over time in predictable ways. Therefore, prospective, longitudinal analyses provide a more nuanced understanding of HNC patients' experiences with depression across time and illness phases.

Baseline/pretreatment depression prevalence estimates range from 17% to 58% (Chen et al., 2009; de Graeff et al., 1999; de Leeuw et al., 2000; Hammerlid et al., 1999; Kelly, Paleri, Downs, & Shah, 2007), with significant variation reported across studies even when the same depression measure (including a diagnostic clinical interview) is utilized. Prospective analyses of depression in HNC patients generally suggest statistically significant increases in depressive symptoms from baseline/pretreatment to during or soon after treatment (Chen et al., 2009; Hammerlid et al., 1999; Kelly et al., 2007). Mild to severe depression appears most common during and immediately following treatment (approximately two to three months following diagnosis), with prevalence ranging from 20–60% (Chen et al., 2009; Hammerlid et al., 1999;

Katz et al., 2004; Kelly et al., 2007). Between six months and one year following diagnosis, statistically significant declines in depressive symptoms are typically observed (de Graeff et al., 1999; de Leeuw et al., 2000), with prevalence of mild to severe depression declining to 17–24% (Chen, Daly, Vazquez, & et al., 2013; de Leeuw et al., 2000; Hammerlid et al., 1999). Such declines may represent a return to pretreatment levels, as indicated by a non-significant difference in depression between baseline and one-year measurements (Hammerlid et al., 1999). Although investigations of depression among long-term HNC survivors are limited, one prospective analysis indicated that the prevalence of mild to severe depression did not differ between one, three, and five years following treatment, remaining at approximately 15% across these time points (Chen et al., 2013). Collectively, these results suggest that depressive symptomatology changes most soon after HNC diagnosis and treatment and then remains relatively stable across the next five years.

Notably, transient depression appears more common than enduring depression, with prevalence rates obtained at single time points exceeding prevalence rates based upon persistently elevated scores across multiple time points (Karnell et al., 2006). Such findings suggest that it is more common for patients to experience depression that resolves after a period of time than it is to experience long-term depression. Across all time points, however, the prevalence of possible to probable depression among HNC patients is higher than the 6.7% prevalence of depression in the general population of the United States (Kessler, Chiu, Demler, & Walters, 2005).

Consistently identified predictors of posttreatment depression include poor condition-specific health-related quality of life (HRQOL) following treatment, presence of pretreatment depressive symptoms, and less time since treatment (Chen et al., 2009; de Leeuw et al., 2000;

Duffy et al., 2007; Hammerlid et al., 1999; Karnell et al., 2006). Age and gender are consistently unrelated to depressive symptoms (Hammerlid et al., 1999; Karnell et al., 2006). Conflicting evidence exists regarding the predictive nature of marital status and disease stage for posttreatment depression (Chen et al., 2009; Duffy et al., 2007; Hammerlid et al., 1999; Karnell et al., 2006).

Assessment

Variation in prevalence estimates is impacted by the timing and approach of depression assessment employed, including method (i.e., self-report versus clinical interview), instrument selection, and basis for severity categorization. When assessed with a diagnostic clinical interview (the Schedule for Affective Disorders and Schizophrenia (SADS)) one month after treatment, depression prevalence in radiation-treated HNC patients was 20% (Katz et al., 2004). Comparative accuracies of three common self-report measures of depression (the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS), and the Centre for Epidemiological Studies-Depression (CES-D) scale) to this clinical interview were high, with area under the curve values of 0.969–0.994 (where optimal accuracy is represented by a value of 1.0) (Katz et al., 2004). Moreover, there were no statistically significant differences between measures, suggesting that each of these three self-report measures provides an accurate basis to screen for clinically significant depression. The authors provided recommendations for thresholds pertaining to severity categorization in HNC patients and suggested that there is little difference in prevalence estimates across these self-report measures, provided that appropriately high cutoff scores are used. The highest levels of sensitivity, specificity, and positive predictive values were found using a cut-off score of 13 on the BDI, 5 on the HADS, and 17 on the CES-D (Katz et al., 2004).

Notably, many diagnostic symptoms of depression overlap with symptoms of physical illnesses and/or their treatment. For example, diagnostic criteria include reduced appetite, significant weight loss (i.e., 5% weight loss in one month), insomnia, reduced activity, and fatigue/anergia (American Psychiatric Association, 2013). This has caused concern that patients experiencing a physical illness may respond to these vegetative items as a reflection of their physical illness, rather than depression, and that responding in this manner could artificially inflate depression scores in these populations. In the medical patient literature, broadly, as well as specifically in the HNC patient literature, consensus does not exist regarding how to address this issue (Katz et al., 2004). Some researchers have advocated for alternative assessment and diagnostic criteria in order to better distinguish depressed from non-depressed medical patients, such as exclusively using cognitive-affective symptoms (e.g., Christensen & Ehlers, 2002; Howren, Christensen, Karnell, & Funk, 2010) or substituting somatic questions with non-somatic alternatives that are less prone to overlap with physical comorbidities (e.g., social withdrawal, lack of reactivity in typically pleasurable situations; the "Endicott Criteria;" Endicott, 1984).

A comparative item response analysis, however, indicated that somatic depressive symptoms largely exhibited the same associations with depression severity (assessed by a diagnostic clinical interview) and with patterns of symptom improvement in depressed patients with and without medical comorbidities (Simon & Von Korff, 2006). Somatic symptoms were neither more weakly associated with overall depression severity nor occurred at lower thresholds of depression in patients with medical comorbidities, compared to those without medical comorbidities. Thus, little evidence of differential item functioning of depression symptoms in medical patients was found. Among HNC patients specifically, the presence of somatic symptoms in depression assessment has not appeared to reduce the accuracy of depression

identification (Katz et al., 2004). HNC research addressing depression has treated this issue in various ways. Most have used the full depression score in analyses (e.g., Chen et al., 2009; de Leeuw et al., 2000; Hammerlid et al., 1999; Karnell et al., 2006), although some authors have focused exclusively on cognitive-affective depression symptoms (e.g., Howren, Christensen, Karnell, & Funk, 2010).

Relationships with Outcomes

Health-related quality of life. HRQOL, a patient-reported measure evaluating objective and subjective aspects of daily functioning and well-being impacted by a disease and its treatment, has increasingly been considered an important outcome of oncological treatment (Funk, Karnell, Christensen, Moran, & Ricks, 2003; McHorney, 1999). Among HNC patients, changes in HRQOL across time parallel changes in depression—HRQOL is characteristically worst during and shortly after treatment, with ongoing improvement and often a return to near-baseline levels one year after diagnosis (Howren et al., 2013). Moreover, experiencing depressive symptoms is reliably associated with reduced general and condition-specific HRQOL (e.g., Duffy et al., 2007; Hammerlid et al., 1999; Karnell et al., 2006; Potash, Karnell, Christensen, Vander Weg, & Funk, 2010). In one of the few prospective analyses of such relationships, baseline depressive symptomatology was a unique independent predictor of poorer HNC-specific HRQOL three and twelve months following diagnosis (Howren et al., 2010). In this study, the presence of relatively mild (subclinical) depressive symptoms prior to treatment negatively affected pretreatment-adjusted HRQOL in all relevant HNC domains (speech, eating, aesthetics, and social disruption), after adjustment for clinical and demographic factors. In another study, depressive symptoms were cross-sectionally associated with HNC-specific functional symptoms (e.g., swallowing, mouth opening, dry mouth, sticky saliva) at baseline and

at one-year, and changes in depressive symptoms across the first year were associated with changes in functional symptoms during that same time (van der Meulen et al., 2013). Clearly, depressive symptomatology is closely associated with patients' functional abilities and subjective attitudes about these abilities.

Mortality. In addition to its relationship with reduced quality of life, elevated depression may be a risk factor for mortality. Meta-analyses conducted across cancer sites have indicated that depression, measured diagnostically or symptomatically either before or after diagnosis, predicts increased mortality (Pinquart & Duberstein, 2010; Satin, Linden, & Phillips, 2009). Given the persistence of these effects after controlling for prognostic medical variables, it has been suggested that depression may play a contributing role in increased mortality (Satin et al., 2009). However, the potential prognostic relationships between psychological well-being and cancer recurrence and survival remain seriously contested (Spiegel & Giese-Davis, 2003). Research regarding such relationships among HNC patients is somewhat limited. In one study, experiencing depression at any time point was associated with HNC recurrence and overall mortality two years after diagnosis, with half of depressed patients, compared to 20% of non-depressed patients, experiencing recurrence or death (Lazure, Lydiatt, Denman, & Burke, 2009). However, this study was limited by a small sample size and lack of distinction between disease recurrence and mortality as outcome measures. More commonly in HNC research regarding this issue, depression and emotional well-being have not demonstrated independent associations with survival or recurrence (Coyne et al., 2007; de Graeff et al., 2001; Mehanna, De Boer, & Morton, 2008).

Depression is more definitively associated with increased mortality by its nature as a risk factor for suicide. Analyses of national databases have indicated that the incidence of suicide is

twice as high among cancer patients than in the general population of the United States (Kendal, 2007; Misono et al., 2008). One such analysis suggested that HNC patients have the highest suicide incidence of any cancer site, a finding that is more pronounced in male compared to female patients (Kendal, 2007). In this study, greater suicide hazards were found for HNC patients who were male, white, and older in age, as well as for patients with oropharyngeal tumors, increased histological grade, distant spread of disease, and contraindication for surgery. Being married was associated with lower suicide hazards. In another comparative analysis, oral cavity/pharynx and larynx represented the cancer sites with the third and fourth highest suicide rates, respectively, with suicide incidence in these patients nearly four times greater than in the general population and comparatively greater than in most other cancer sites (Misono et al., 2008). Identification of and intervention for depression are essential for optimization of HNC patients' quality of life and prevention of suicide, and potentially could impact disease survival.

CHAPTER 3: WEIGHT LOSS IN HEAD AND NECK CANCER PATIENTS

Prevalence

Unintentional weight loss before HNC diagnosis is common. A recent meta-analysis reported that 20.2% (±2.9%) of HNC patients present with significant UWL (UWL ≥ 5% in 1 month or ≥ 10% in 6 months) at diagnosis (Couch et al., 2014). It is more common to lose > 10% of body weight, compared to only 5–10%, in the six months preceding diagnosis, and on average patients lose 10% of their body weight during this time (Datema et al., 2011; Lees, 1999). Furthermore, Couch and colleagues' (2014) meta-analysis indicated that the prevalence of significant UWL increases from 20.2% to 32.3% (±4.9%) when assessed at the time of treatment initiation.

Regardless of treatment modality, it is common for patients to experience a decline in energy intake and significant weight loss during treatment (van den Berg et al., 2006). Statistically significant weight loss has been reported during radiation treatment, with 25–32% of patients losing 5% of their body weight during the time between diagnosis and conclusion of treatment (Beaver, Matheny, Roberts, & Myers, 2001; Nourissat et al., 2010). Among a sample of patients treated with diverse modalities (alone or in combination), 71% experienced 5% UWL by the end of treatment, with an average of 9% UWL (Kubrak, Olson, & Baracos, 2013). It appears that degree of weight loss is greatest for patients treated with a combination of chemotherapy and radiation, with reports of these patients losing an average of 10% of pretreatment body weight during treatment (Newman, Vieira, Schwiezer, & et al., 1998) and up to 42% of patients experiencing more than 20% UWL by 30 days posttreatment (Capuano et al., 2008).

In the months following HNC treatment, weight loss continues despite increased energy intake (Couch et al., 2014; Kubrak et al., 2013; van den Berg et al., 2006). Despite full oral

intake and resumption of baseline energy intake, 88% of patients continued to lose weight nearly three months after treatment (Kubrak et al., 2013). By six months after radiation for advanced HNC, 66% of patients have experienced UWL > 10% and 26% have a body mass index (BMI) < 20 (Silander, Nyman, & Hammerlid, 2013). The percentage of weight loss has been observed to increase over time for up to a year following treatment, moving from an average of 5% UWL after three weeks of radiation to 17% UWL one year posttreatment (Larsson et al., 2005). However, treatment modality may influence the duration and trajectory of weight loss. Pooled prevalence estimates from a recent meta-analysis indicated that percentage weight loss peaked three months after treatment for chemoradiation-treated patients and six months after treatment for radiation-treated patients (Couch et al., 2014). Another report indicated that surgically-treated patients had regained weight to near-baseline levels at six months posttreatment, yet patients treated with radiation or a combination of modalities maintained their UWL and did not experience weight regain (van den Berg, Rasmussen-Conrad, van Nispen, van Binsbergen, & Merkx, 2008). With proactive nutritional guidelines in place, average percentage weight loss can decline by three months posttreatment and weight loss can stabilize by six months posttreatment (Brown, Ross, Jones, Hughes, & Banks, 2014).

Significant weight loss has been reported across samples that include patients of all HNC stages and sites. Such weight loss is not solely a pretreatment occurrence, nor is it only associated with certain sites or treatment modalities. The reviewed research indicates that weight loss is common during the months preceding HNC diagnosis, during treatment, and in the months following treatment. Although variability exists in the duration and trajectory of continued weight loss after treatment, the literature suggests that weight loss typically stabilizes or begins to reverse approximately six months after diagnosis.

Relationships with Outcomes

Malnutrition. UWL is a relevant outcome in HNC due to its indication of potential malnutrition. Consensus regarding the definition and assessment of malnutrition is lacking in the general medical (Meijers, van Bokhorst-de van der Schueren, Schols, Soeters, & Halfens, 2010) and cancer literatures (Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2003), as well as HNC-specific literature (Silander et al., 2013; van Bokhorst-de van der Schueren et al., 1999). Despite ongoing debate regarding appropriate cutoff values and lack of a recognized gold standard operationalization of malnutrition, nutrition experts have collectively agreed that UWL, BMI, and lack of nutritional intake are the most important criteria to consider (Meijers et al., 2010). HNC patients are considered to face unique risk for malnutrition due to the common presence of multiple contributing factors (Chasen & Bhargava, 2009; Couch et al., 2007; Datema et al., 2011; Silander et al., 2013). Malnutrition at diagnosis may be impacted by history of alcohol or tobacco use or poor nutritional habits. Furthermore, the situation of tumors in the upper aerodigestive tract may obstruct or provoke pain when performing eating-related functions, such as chewing and swallowing, which may impact nutritional intake at time of diagnosis. Moreover, treatment-related toxicities and side effects, such as mucositis, xerostomia, and pain, can cause further eating-related impairments. Depending on the method of assessment and cutoff used, 20–67% of HNC patents are malnourished, or at high risk of becoming malnourished, at diagnosis (Brown et al., 2014; Kubrak et al., 2010; Ravasco, Monteiro-Grillo, & Camilo, 2003; van Bokhorst-de van der Schueren et al., 1997). In a comparative study of eight cancer sites, the prevalence of malnutrition in HNC patients at diagnosis was the second highest, behind stomach cancer (Ravasco, Monteiro-Grillo, & Camilo, 2003).

UWL has been considered to be "the most accepted criterion for malnutrition" (van den Berg et al., 2008, p. 835). However, various values and time frames of UWL have been employed as bases for malnutrition or critical weight loss categorization in HNC patients. Most commonly, presence or risk of malnutrition in HNC is based upon UWL greater than or equal to 10% during the previous six months (Beaver et al., 2001; Capuano et al., 2008; Datema et al., 2011; Petruson, Silander, & Hammerlid, 2005; Ravasco, Monteiro-Grillo, Vidal, et al., 2003; Silander et al., 2013; van Bokhorst-de van der Schueren et al., 1997; van den Berg et al., 2008; van den Berg et al., 2006). Some HNC researchers consider the six months prior to diagnosis, and rely upon patient-reported prediagnosis weight loss, whereas others use diagnosis as a baseline and prospectively measure weight for six months. The other commonly used UWL-based classification of malnutrition risk entails UWL greater than 5% within one month (Beaver et al., 2001; Capuano et al., 2008; Silander et al., 2013; van den Berg et al., 2006), three months (Capuano et al., 2010; Silander et al., 2013), or during the course of treatment (Nourissat et al., 2010). Relatedly, BMI < 20 (Hammerlid et al., 1998; Ravasco, Monteiro-Grillo, Vidal, et al., 2003; Silander et al., 2013) or a 7% loss of BMI in a six-month period (Beaver et al., 2001) have been considered indicative of malnutrition. The predictive properties of UWL have been compared to alternate indicators of nutritional status. In a sample of head and neck and other cancer patients, percentage UWL demonstrated superior sensitivity and specificity and was the best indicator of nutritional depletion (Ravasco, Monteiro-Grillo, Vidal, et al., 2003). Overall, the literature indicates that UWL is the best stand-alone measurement of nutritional depletion in HNC patients (Brown et al., 2014; Ravasco, Monteiro-Grillo, Vidal, et al., 2003).

Cachexia. Significant weight loss is also a clinically relevant indication of cancer cachexia. Although a diagnosis of cachexia is informed by UWL, weight loss represents just one

facet of cachexia. In addition to reduced nutritional intake and UWL, cachexia is characterized by multifaceted factors including an inflammatory response, loss of skeletal muscle mass ("wasting"), abnormal metabolism, and progressive impairment in functioning (Blum et al., 2011; Couch et al., 2014; Couch et al., 2007; Fearon et al., 2011). Moreover, cancer cachexia does not respond to nutritional intervention in the manner in which malnutrition does (Blum et al., 2011; Couch et al., 2014; Couch et al., 2007; Fearon et al., 2011). For a detailed comparison of the differences between cachexia and malnutrition in HNC patients, see Couch et al. (2007) and Couch et al. (2014).

Although multiple definitions of cachexia have been published (Argilés et al., 2010; Evans et al., 2008; Fearon et al., 2011), UWL is included as a prominent clinical feature in each. Given its ease of measurement in clinical settings, UWL has been identified as an appropriate initial screening tool for HNC cachexia (Couch et al., 2014). Furthermore, degree (percentage) of weight loss has been suggested as a basis for cachexia severity classification (precachexia: $\leq$ 5% UWL, mild cachexia: > 5% UWL, moderate cachexia: > 10% UWL, and severe cachexia: 15% UWL (Argilés et al., 2010; Blum et al., 2011; Fearon et al., 2011). However, it is clear that the presence of UWL is not sufficient in itself to suggest HNC cachexia (Couch et al., 2014).

Despite the delineations between malnutrition and cancer cachexia, their common marker of UWL can obfuscate their classification in the literature and upon clinical presentation. UWL remains an important parameter that is easily utilized for initial screening for both conditions in clinical practice. However, whereas decreased nutritional intake and UWL are the most important criteria in malnutrition, UWL is one of several factors in cancer cachexia. The significance of UWL for cancer cachexia primarily lies in its utility as an initial screening tool and basis for severity classification.

Survival. The prognostic value of UWL in HNC patients has been compared to other established nutritional parameters such as body fat and lean body mass measurements, percentage of ideal body weight, serum albumin, total lymphocyte count, and a nutritional index score (which combines several of these measures). Among all of these parameters, UWL > 5% during the six months preceding treatment was the best predictor of three-year HNC survival (van Bokhorst-de van der Schueren et al., 1999). Furthermore, UWL > 10% during the six months prior to surgery was the best predictor of major post-operative complications, and was associated with a 50% chance of experiencing major complications (van Bokhorst-de van der Schueren et al., 1997). Several studies have identified pretreatment weight loss > 10% to be an independent predictor of decreased overall survival in HNC patients, with less severe UWL (5–10%) also associated with poorer overall survival (for a review, see Couch et al., 2014). One such study reported that the distinction between the overall survival of patients who were severely malnourished at diagnosis and those who were not was present for 10 years, with malnourished patients having a 1.8 times higher relative risk of death and lower overall survival probabilities (Datema et al., 2011). These results suggest that, among HNC patients, UWL of 5–10% has superior prognostic value to other nutritional indicators. In addition to the implications of the severity of weight loss, the pattern/trajectory of weight change after diagnosis appears influential. Karnell, Sperry, Anderson, & Pagedar (2014) recently found that HNC patients with stable weight values at 3-month follow-up had the highest five-year survival rates (72.6%), compared to patients who lost or gained weight $\geq$ 5% of their weight during this time. UWL appears to be a sensitive and specific assessment of risk, with predictive power for HNC survival and complications.

Predictors

To enable provision of early nutritional support and enhance patient well-being and survival, early identification of patients at risk of significant weight loss is beneficial. The disease- and treatment-related characteristics that are commonly associated with severe weight loss in HNC patients are advanced disease stage, site, and treatment modality. Critical weight loss (5–10%) appears more common and greater in magnitude with each advancing disease stage (Brown et al., 2014; Couch et al., 2014; Karnell et al., 2014; Nourissat et al., 2010; Petruson et al., 2005; Ravasco, Monteiro-Grillo, Vidal, et al., 2003), with one study reporting that stage explained 10% of the variance in UWL during treatment (van den Berg et al., 2008). Such associations apparently reflect the influence of tumor burden on the presence of nutritional deterioration. However, not all studies have found this relationship between stage and weight loss (Beaver et al., 2001; Britton et al., 2012; Hammerlid et al., 1998; Newman et al., 1998; van den Berg et al., 2006). Furthermore, there is typically a higher degree of weight loss for patients with cancers of the pharynx, larynx, and oral cavity (prevalence of significant weight loss > 30%), compared to cancers of the paranasal sinuses, nasal cavity, and salivary glands (Beaver et al., 2001; Britton et al., 2012; Brown, Brauner, & Minnotte, 1993; Couch et al., 2014; Nourissat et al., 2010; Petruson et al., 2005). As discussed previously, treatment modality may be associated with variability in duration of weight loss following treatment. Furthermore, treatment modality appears to be associated with magnitude of weight loss. Patients treated with radiation or with multiple modalities tend to experience the most weight loss, with the combination of chemotherapy and radiation appearing to be particularly harmful (Beaver et al., 2001; Brown et al., 2014; Couch et al., 2014; Silander et al., 2013; van den Berg et al., 2006). In one study, patients treated with a combination of chemotherapy and radiation had a nearly five

times higher risk of UWL > 10%, the highest of any predictive odds ratio, compared to patients treated with radiation alone or surgery and radiation in combination (Silander et al., 2013). Dose and fractionation schedule of radiation have not been associated with severe weight loss (Beaver et al., 2001; Britton et al., 2012). Importantly, patients who present with advanced stage tumors often also experience more aggressive or multimodal treatment, which can compound the factors affecting weight loss. Individually and collectively, symptoms such as dysphagia, xerostomia, thick saliva, difficulty chewing, and mouth pain predict weight loss (Farhangfar et al., 2014; Kubrak et al., 2013).

Age, race, gender, and history of tobacco and alcohol use have not been independently associated with severe weight loss (Beaver et al., 2001; Nourissat et al., 2010; Silander et al., 2013; van den Berg et al., 2006). Significant prediagnosis weight loss has typically been associated with severe weight loss during treatment (Beaver et al., 2001); however, it has also been reported that patients with significant weight loss at diagnosis had decreased odds of subsequent weight loss (Brown et al., 2014) or no significant relationship with later weight loss (Nourissat et al., 2010; Silander et al., 2013). Higher weight or BMI at diagnosis has been identified as a predictor of UWL during radiation treatment (Nourissat et al., 2010) as well as three (Brown et al., 2014; Karnell et al., 2014) and six (Silander et al., 2013) months following diagnosis. Compared to normal or underweight patients, those who were overweight (BMI 25–30) or obese (BMI > 30) at diagnosis had 1.82 and 3.49 greater odds, respectively, of losing at least 10% of their body weight three months later (Brown et al., 2014). This predictive effect of BMI > 25 remained six months after diagnosis, when the odds for > 10% UWL increased by 14% for each 1.0 increase in BMI (Silander et al., 2013). Similarly, pretreatment BMI may predict which patients actually lose, versus gain, weight. HNC patients who lost ≥ 5% of

pretreatment weight at a 3-month follow-up were more likely to have been overweight or obese (BMI $\geq$ 25) pretreatment, whereas those who gained $\geq$ 5% were more likely to have been underweight (BMI < 18.5) (Karnell et al., 2014). However, initial weight or BMI are not always predictive of later weight loss (van den Berg et al., 2006).

Further research is needed to understand the identification and impact of significant weight loss in patients with high weights and/or BMIs. Significant weight loss may go undetected in higher BMI patients, potentially because health care providers and/or patients may see the weight loss as acceptable or even healthy (Brown et al., 2014). Furthermore, it has been suggested that these patients may be able to tolerate higher percentages of weight loss before experiencing nutritional impairment (Brown et al., 2014). Recent publications have reported both that overweight or obese HNC patients had better (Karnell et al., 2014) and worse (Iyengar et al., 2014) survival than patients with normal or underweight pretreatment BMIs. BMI may differentiate for whom weight loss has negative survival implications. Among nasopharyngeal cancer patients, weight loss $\geq$ 5% was only associated with reduced survival in patients with underweight and normal BMIs, and not among overweight or obese patients (Shen, Chen, Li, Gao, & Xia, 2013).

Importantly, obese cancer patients present with substantial variability in proportions of fat and lean tissue, and these various body compositions have been differentially related to functional and survival outcomes (Prado et al., 2008). In particular, depletion of lean muscle mass is an independent prognostic indicator of decreased survival among obese cancer patients (Prado et al., 2008). Obese patients with loss of muscle mass live 10 months less than obese patients without loss of muscle mass (Prado et al., 2008). This severe muscle atrophy can exist in the presence of obesity, and is potentially masked by high body weight and adipose tissue.

Notably, this depletion may or may not be reflected in UWL, as obese individuals with and without loss of skeletal mass have not differed in their degree of UWL (Prado et al., 2008). Although the nutritional significance of UWL in obese patients may not be fully known without accompanying analyses of body composition, paying less attention to obese patients' weight loss risks failing to identify patients at risk for poor outcomes. Investigation of whether the weight loss entails loss of fat or body mass is likely to be of particular prognostic importance in obese patients (Brown et al., 2014; Prado et al., 2008).

CHAPTER 4: RELATIONSHIPS BETWEEN DEPRESSION AND NUTRITION

Review of Existing Literature in Various Patient Populations

Inverse associations between depression and nutritional status have been reported across diverse patient populations, using various nutritional parameters (i.e., UWL, serum albumin, BMI, anthropometric measurements, and patient-reported screening tools). Cross-sectionally, higher depression scores have been associated with poorer nutritional markers among patients with metastatic lung cancer (Giannousi et al., 2012), advanced prostate cancer (Toliusiene & Lesauskaite, 2004), chronic kidney disease (Kalender, Ozdemir, & Koroglu, 2006; Koo et al., 2003), and inflammatory bowel disease (Addolorato, Capristo, Stefanini, & Gasbarrini, 1997). In a study that identified depression as the strongest demographic or psychosocial predictor of nutritional risk in colorectal cancer patients, depressed patients had 5.6 times greater odds of being in a higher nutritional risk category than non-depressed patients (Daudt, Cosby, Dennis, Payeur, & Nurullah, 2012).

Additionally, such associations have been studied in geriatric populations. As with HNC patients, depression and poor nutritional status are each common and associated with negative outcomes among older adults (Smoliner et al., 2009). Cross-sectionally, depression has been associated with poorer nutritional parameters among elderly outpatients (Cabrera, Mesas, Garcia, & de Andrade, 2007; Callen & Wells, 2005; Saka, Kaya, Ozturk, Erten, & Karan, 2010; Ülger et al., 2010; van Bokhorst-de van der Schueren et al., 2013), hospitalized (German et al., 2008), recently hospitalized (Chen, Huang, & Chen, 2014) elderly patients, and nursing home residents (Smoliner et al., 2009). Odds ratios associated with these results suggest that elderly patients with elevated depression scores have a 1.6 to 4.38 times increased risk of experiencing nutritional deficit, compared to their non-depressed counterparts (Cabrera et al., 2007; Callen &

Wells, 2005; Ülger et al., 2010; van Bokhorst-de van der Schueren et al., 2013). One study suggested that depression is the most common identified cause of UWL among nursing home residents, accounting for 36% of cases (Morley & Kraenzle, 1994). The only study to analyze the reverse association, that of nutritional status predicting depression, indicated that undernourished patients were 2.23 times more likely to experience depression than patients with normal nutritional statuses (German et al., 2008).

Across populations, several cross-sectional studies have noted the difficulty of establishing a causal relationship between depressive symptoms and nutritional status and have identified the need to further elucidate directionality in future research (Chen et al., 2014; Smoliner et al., 2009). It has been suggested that depression could be either the "cause or consequence" of impaired nutritional status (Smoliner et al., 2009, p. 1666) and that a reciprocal/bidirectional relationship may exist, such that the two domains simultaneously influence each other (Chen et al., 2014; Smoliner et al., 2009). Although prospective assessments of relationships between depression and nutritional markers across time are limited, the existing research provides some indication that depression predicts poorer nutritional status, rather than the reverse temporal relationship. Among patients with end-stage renal disease, changes in depression and serum albumin were assessed over six months and models predicting the influence of depression on albumin and albumin on depression (while controlling for disease severity) were compared (Friend, Hatchett, Wadhwa, & Suh, 1997). Friend and colleagues (1997) found that initial depression scores predicted decreases in albumin across time, yet initial albumin levels did not predict changes in depression, suggesting that depression influenced nutritional status rather than the reverse case. Similarly, a prospective analysis of older adults reported that patients with more depressive symptoms prior to discharge from a prolonged

hospitalization were more likely to experience nutritional deterioration six months later (Chen et al., 2014). Importantly, depression has remained associated with poor nutritional status when the somatic symptoms of depression are excluded from analyses (Friend et al., 1997; Kalender et al., 2006; Koo et al., 2003), as well as after controlling for factors such as disease severity, age, and functional status (Friend et al., 1997; Koo et al., 2003; Smoliner et al., 2009; van Bokhorst-de van der Schueren et al., 2013). Although authors of this literature typically suggest that it may be the presence of prior psychological depression, rather than disease-related factors, that influences subsequent nutritional outcomes (Friend et al., 1997), further longitudinal research that explores the complexity of these relationships is needed.

Review of Existing Literature in Head and Neck Cancer Patients

More than 25 years ago, Westin and colleagues (1988) first reported that depression was significantly associated with impaired nutrition among head and neck cancer patients at least one year posttreatment. In this sample, patients categorized as depressed by a clinical interview were significantly more likely to be malnourished (defined, in part, by UWL) than not. Despite this early suggestion of a meaningful relationship between depression and nutritional factors in HNC patients, surprisingly little research has been conducted regarding these topics in the time since. Most notably, a recent prospective study identified depression during the first week of radiation treatment as an independent predictor of malnutrition four weeks after the conclusion of treatment (Britton et al., 2012). Depression, whether measured with continuous symptoms or a categorical clinical cutoff score, predicted malnutrition after controlling for patient age and gender, tumor site and stage, number of radiation fractions, presence of a caregiver, presence of a feeding tube, and a dietician-conducted clinical assessment of malnutrition. Britton and colleagues (2012) stated that their findings suggest not only that depression is a factor in the

nutritional decline of HNC patients treated with radiation, but furthermore that it is a stronger predictor than several commonly accepted clinical risk factors (i.e., tumor stage, radiation fractionation amount, feeding tube status, caregiver presence, and dietician-conducted clinical assessment). The authors cautioned that the potential clinical implications of their results are precluded by replication of their findings, as well as expanded research investigating whether depression functions as a cause, or rather an indicator of, malnutrition.

Though intriguing, Britton and colleagues' (2012) study has important limitations. First, the ultimate utility of predicting nutritional status so soon after the conclusion of treatment is debatable. The latest time point in Britton and colleagues' (2012) longitudinal cohort design was four weeks post-radiation treatment, which may preclude the ability of the study to capture relationships with meaningful, long-term nutritional implications. Additionally, depression was measured with the Patient Health Questionnaire-9 (PHQ-9), and there was overlap between the PHQ-9 item addressing UWL and UWL that was utilized as part of the study's nutritional outcome variable. Furthermore, Britton and colleagues' (2012) small sample ($N = 58$) and exclusive focus on patients treated with radiation limits the generalizability of their results to HNC patients with diverse treatment experiences and treatment-related side effects.

Additional investigations regarding the nature of associations between depression and markers of nutritional compromise, including UWL, among HNC patients are quite limited. Britton and colleagues' (2012) analysis stated that "no other studies have reported on the relationship between depression and malnutrition in HNC" (p. 340). Although these authors' work certainly represents the most comprehensive analysis of the prospective relationship between depression and nutrition in HNC, additional studies have measured related constructs. A recent study reported that depressive symptoms predicted energy intake and weight loss 2.5

months after HNC treatment (Kubrak et al., 2013). In this study, patients' reports of the frequency of depressed mood and the severity of its interference with eating were associated with outcomes, such that depression was a significant predictor of reduced nutritional intake (in univariate and multivariate models) and a significant predictor of weight loss (univariate models only). Unfortunately, this study assessment of depressive symptoms using two questions addressing mood during the previous three days was not a methodologically strong assessment of depression. Another analysis of predictors of weight loss in HNC patients reported a non-significant trend for higher depression prevalence in malnourished patients (defined by UWL $\geq$ 10% in six months) at each time point, up to three years post-diagnosis (Petruson et al., 2005). Depression was not, however, an independent predictor of UWL in regression analyses in this small sample. In a cross-sectional analysis of mixed cancer patients, including HNC, higher scores on an anxiety/depression scale were associated with poorer nutritional status and reduced energy intake at the end of radiation treatment (Ravasco, Monteiro-Grillo, & Camilo, 2003). The combination of anxiety and depression, as well as patients with various types of cancer, precludes the ability of this study to yield significant conclusions regarding relationships between depression and nutritional variables in HNC patients. However, these results are consistent with Kubrak and colleagues' (2013) findings in HNC.

Potential Mechanisms for Associations

Empirical investigations into the mechanisms operating behind the observed associations between depression and nutritional outcomes have not been conducted. However, several authors have hypothesized about the nature of these relationships. Particularly relevant characteristics of depression include reduced appetite and nutritional intake, reduced self-care behaviors, anhedonia, and decreased interest in social or eating-related activities. Patients who

are experiencing depression may take poorer care of themselves, which, particularly in the context of HNC, may manifest as reduced nutritional intake (Britton et al., 2012) and/or reduced adherence to nutritional supplementation regimens, rehabilitative exercises (e.g., for swallowing), and adapting food preparation methods. Furthermore, depression in HNC patients can entail social withdrawal and not wanting to eat in the presence of others, which could negatively impact nutritional intake (Chasen & Bhargava, 2009).

Fewer authors have suggested the inverse temporal precedence relationship, that nutritional factors may influence psychological functioning (Britton et al., 2012; Chasen & Bhargava, 2009; Ravasco, Monteiro-Grillo, Marques Vidal, & Camilo, 2005; Ravasco, Monteiro-Grillo, Vidal, & Camilo, 2004). When this relationship has been discussed, it has been in the context of recognizing an inability to determine whether psychological functioning influences or is influenced by nutritional changes. Chasen and Bhargava (2009), however, suggested that malnutrition contributes to the high rates of suicide among HNC patients through its impact on emotional functioning. Patients who experience significant nutritional deterioration early in the HNC experience could respond to such a rapid decline in physical health with an "existential crisis" characterized by depressed mood and hopelessness (Larsson et al., 2005) p. 426). Alternatively, patients may have poorer body images in response to nutritional deterioration and early weight loss, and poorer body image following HNC is associated with higher depressive symptoms across time (Rhoten, Deng, Dietrich, Murphy, & Ridner, 2014).

Of the various mechanisms that investigators have suggested for depression impacting the development of nutritional compromise or vice versa, the majority could theoretically operate in either temporal precedence direction or in a bidirectional manner. For example, depression may behaviorally manifest as social withdrawal or not wanting to eat around other people, which

ultimately contributes to weight loss (i.e., temporal precedence of depression). However, the inverse (i.e., temporal precedence of nutritional impairment) may also be true. Patients experiencing nutritional compromise often have difficulty with eating-related functions, such as chewing, swallowing, and saliva production, or may be unable to have oral nutritional intake, and may not be inclined to eat in the presence of others. The social withdrawal and isolation that occur in response to these nutritional challenges can influence the onset of depression.

Rather than be characterized by one of these temporal precedence associations (i.e., depression predicting subsequent weight loss or weight loss predicting subsequent depression), the association between depression and nutritional compromise in HNC patients could ultimately be conceptualized as a bidirectional relationship in which the two domains reciprocally influence each other (Britton et al., 2012). This complex, dynamic relationship has not previously been evaluated. Importantly another variable, such as disease severity or functional impairment, could impact both depression and nutritional status. As such, it is critical to include disease- and treatment-related factors when analyzing these relationships. Although depression and weight loss have long been linked diagnostically, there is a limited understanding of how these constructs influence each other over time. An enriched understanding of these longitudinal associations is particularly important in a population for which depression is common and nutritional functioning is a critical outcome.

Statistical Considerations

Previous studies assessing these relationships have exclusively employed traditional linear regression-based statistical analyses. However, the ability of linear regression-based approaches to detect nuanced longitudinal changes is limited by their assessment of average change across entire samples and lack of consideration of quadratic relationships. Growth curve

modeling (GCM) offers a promising and novel approach for addressing such issues. GCM techniques model the average population-level trajectory of change (growth curve), but also allow individual patients' trajectories to vary from this average growth curve (DeLucia & Pitts, 2006). If individual variability exists, GCM assesses whether this is influenced by certain theoretically informed predictor variables. GCM examines both the level of the outcome variable at a certain point in time (intercept) and the rate of change in the outcome over time (slope), and assesses predictors of variability in each of these parameters (DeLucia & Pitts, 2006). The following questions are addressed in GCM: a) does change occur over time, on average, b) what is the average shape of change over time (e.g., linear or curvilinear, increasing or decreasing), c) do individual patients change at different rates, and d) which patient-level characteristics, if any, predict individual variability in the rate of change (DeLucia & Pitts, 2006).

There are multiple advantages to GCM relative to analytic techniques that assess average change across an entire sample. In GCM, time points are nested within participants, which permits analysis of within-subject change in addition to between-subject differences in change. Interdependence among repeated measures (within subjects) is also addressed. As such, within-subject change across time (individual trajectories or growth curves) can be modeled, between-subject differences in these individual trajectories can be examined, and predictors of growth curve variability can be identified (Raudenbush, 2001). Although other analytic techniques assess differences in *degree/amount* of change based upon a predictor, GCM uniquely allows researchers to account for individual differences in *rate* of change based upon a predictor variable (DeLucia & Pitts, 2006). Additionally, participants with missing data (repeated measures) can be retained in analyses. By facilitating modeling of individual growth curves for

each participant, GCM is a valuable technique for analyzing longitudinal data. For further comparison of GCM and more traditional regression techniques for analyzing longitudinal data in psychological studies, see (DeLucia & Pitts, 2006).

CHAPTER 5: SPECIFIC AIMS

As previously discussed, two potential models of temporal precedence for the association between depressive symptoms and weight loss exist. Specific Aim #1 addressed hypotheses regarding the primary expected temporal model, which predicted that baseline depressive symptoms would be associated with subsequent weight loss outcomes. Specific Aim #2 addressed the alternative model, that of early weight loss predicting later depression outcomes. Both models used the 6-month assessment as the intercept time point.

Specific Aim #1: To examine whether baseline depression symptoms predict: (a) total percentage weight loss at the 6-month follow-up, and (b) rates of change in percentage weight loss from 0 to 12 months. My hypothesis was that patients with higher depression symptom scores at diagnosis would experience (a) higher total percentage of weight loss at 6 months, and (b) greater negative curvilinear change in percentage weight loss. As such, it was expected that rates of acceleration/deceleration (quadratic change) in percentage weight loss, or instability in weight over time, would be differentiated by levels of baseline depression. In contrast, less depressed patients were expected to experience relative stability in weight over time.

> **Sub-Aim #1.1: If there was a main univariate effect of baseline depressive symptoms, to evaluate whether depressive symptoms predicted weight loss outcomes above and beyond the effects of other established HNC-related weight loss risk factors.** My hypothesis was that baseline depressive symptoms would demonstrate incremental predictive utility for (a) total percentage weight loss at 6 months and (b) rates of change in percentage weight loss, beyond other

clinical factors that were significantly correlated with depression and weight loss in preliminary analyses.

Specific Aim #2: To examine whether early weight loss predicted levels of depression symptoms from 0 to 12 months. These analyses examined the possibility that degree of early weight loss (between baseline and 3 months) differentiated overall levels of depressive symptoms across time.

Sub-Aim #2.1: If there was a main univariate effect of early weight loss, to evaluate whether early weight loss predicted depressive symptoms above and beyond the effects of other clinical and demographic factors. This analysis examined whether early weight loss demonstrated incremental predictive utility for levels of depression from baseline to 12 months, beyond other factors that were significantly correlated with depression and weight loss in preliminary analyses.

CHAPTER 6: RESEARCH DESIGN AND METHODS

Participants and Procedures

The research employed a prospective cohort design. Participants were adults (age 18 or older) diagnosed with upper aerodigestive tract carcinomas and recruited from the University of Iowa Hospitals and Clinics' (UIHC) Department of Otolaryngology–Head and Neck Surgery for enrollment in the department's Outcomes Assessment Project (OAP). Enrollment occurred at patients' initial clinic visits, at which time they were approached by research staff, offered participation in a longitudinal study of cancer-related outcomes, and consented in writing if interested. Enrollment in the OAP began in February 1998 and ended in October 2013. Of the patients who met OAP eligibility criteria during this time frame, 76.0% enrolled in the study, 5.5% refused participation, and 18.5% were missed (i.e., not approached). Through September 2013, the OAP had 2,377 enrolled patients, with observed all-cause survival rates of 91.8% at 9-month follow-up and 88.0% at 12-month follow-up. Because measurement of depressive symptoms was not included in the OAP survey battery for patients enrolled between December 1999 and November 2001, patients who were initially enrolled in the OAP during this time were not eligible for inclusion in the present analyses (n = 194), thereby reducing the overall eligible sample to 2,183 patients. Actual enrollment dates for patients included in the present study were March 1998–October 1999 and November 2001–July 2013.

OAP data represents a combination of patient- and provider-reported data (e.g., treatment modality, survival outcome, demographic information, and clinical and psychosocial characteristics), as well as information extracted from patients' medical charts (e.g., cancer site and stage, height, and weight). This information is collected at the time of enrollment (i.e., at time of diagnosis and before initiation of oncologic treatment; "baseline") and at follow-up clinic

visits 3, 6, 9, and 12 months after diagnosis. Although recruitment of new patients has concluded, the project continues ongoing longitudinal analysis of HNC treatment outcomes in enrolled patients. All study procedures were approved by the University of Iowa Institutional Review Board.

The sample for the present study consisted of OAP participants with measurements of weight and depression symptoms at baseline and at a minimum of one additional time point (3-, 6-, 9-, or 12-month follow-up). The statistical analyses employed for this study used all available data for each patient, but allowed for missing data beyond the above-stated criteria. Of the 2,183 OAP patients, 564 met this inclusion criteria and were evaluated in the present analyses. For clinical and demographic characteristics of these patients, see Table 1. The sizeable number of excluded patients is largely due to these analyses' inclusion requirement of repeated assessments and the nature of attrition in the OAP sample. No systematic reasons for attrition that could affect key variables in the present study were noted. A primary identified reason for attrition in the OAP is the rural nature of the population. Patients who travel large distances to receive primary oncological treatment at UIHC often undergo follow-up care at a separate local clinic. Although these patients are still mailed their surveys at each appropriate study follow-up time point, completion requires a higher degree of patient effort (compared to patients who complete the measures in-person at the time of their follow-up visits at UIHC).

Background Measures

Demographic and clinical variables. Sociodemographic information was collected upon enrollment in the OAP and updated at each time point as applicable. Accessible demographic information included gender, age, race/ethnicity, and marital status. Furthermore, cancer site, stage, recurrence status, and treatment modality were documented upon enrollment.

Table 1

Descriptive Statistics for Demographic and Clinical Variables

Variable	Mean (*SD*)
Age at diagnosis	60.47 (12.3)
BMI	27.45 (6.36)
Variable	n (%)
Male	356 (63.1)
Married	367 (65.1)
Caucasian	528 (96.7)
Cancer site	
Oral cavity	233 (41.3)
Oropharynx	120 (21.3)
Hypopharynx	24 (4.3)
Larynx	101 (17.9)
Other/unknown	86 (15.2)
Disease stage[a]	
Early (0-II)	212 (37.6)
Advanced (III- IV)	312 (55.3)
Not stageable/unknown	40 (7.1)
Treatment modality	
Surgery only	206 (36.5)
Radiation or chemotherapy only	57 (10.1)
Surgery & Radiation	146 (25.9)
Radiation & Chemotherapy	72 (12.8)
Surgery & Chemotherapy	2 (0.4)
Surgery, Radiation, & Chemotherapy	31 (5.5)
None/unknown	50 (8.9)
Recurrence status at diagnosis	
Primary cancer	469 (83.2)
Recurrent cancer	62 (11.0)
Persistent cancer	12 (2.1)
Tobacco use at diagnosis	
Current	153 (27.6)
Previous	265 (47.7)
Never	137 (24.7)
Alcohol use status at diagnosis (MAST)	
Problem drinker	98 (17.4)
Possible alcoholic	47 (8.3)
Nonalcoholic	312 (55.3)
Unknown	107 (19.0)

Note. All variables are collected at baseline (pretreatment) assessment.

[a] Represents pathological stage; if unavailable, represents clinical stage.

Cancer site was categorized as oral cavity, oropharynx, hypopharynx, larynx, or other. Disease stage was coded as I–IV, with higher stages indicative of more extensive disease. For the present analyses, pathological stage was used if available, otherwise clinical stage was used. Stages I–II were coded as *early* and stages III–IV were coded as *advanced*. Although the vast majority of patients first present at UIHC and enroll in the OAP with an initial primary HNC tumor, a limited number present for treatment with a recurrence of a primary tumor that was previously treated elsewhere. Thus, recurrence status at diagnosis was coded as *recurrence* or *non-recurrence*. Treatment modality was coded as radiation only, chemotherapy only, surgery only, or a combination of these modalities.

Self-report measures. At each time point, patients reported on current use of a gastric feeding tube and dietary status (i.e., oral intake abilities/restrictions). For dietary status, the response options were condensed into *nothing by mouth (NPO)* versus *not-NPO*. Pain was also assessed at each time point, with patients choosing a number 0–10 to describe the degree of pain they experienced during the past four weeks (where 0 represents "No pain" and 10 represents "Worst Possible Pain"). Patients reported on their past and present tobacco and alcohol use upon enrollment, and reported on current use at each time point. If current or previous tobacco use was endorsed, patients were asked to report the total number of years used. Similarly, if current or previous alcohol use was endorsed, patients reported the total number of years used. Furthermore, alcohol abuse was assessed at diagnosis with the Michigan Alcohol Screening Test (MAST). Subjects who scored a three or higher on this survey were classified as problem drinkers (Selzer, Vinokur, & Rooijen, 1975).

Head & Neck Cancer Inventory (HNCI; see Appendix A) (Funk et al., 2003). Eating-related HRQOL was measured at each time point using the eating subscale of the HNCI. The

HNCI is a self-report measure consisting of 29 items that assess HRQOL across four HNC-specific domains: eating, aesthetics, speech, and social disruption. Uniquely, the HNCI assesses both functional (i.e., patient's level of functioning) and attitudinal (i.e., patient's satisfaction with level of functioning) aspects of HRQOL. Only the eating scale score was utilized due to its particular relevance for the present study. The eating domain consists of 10 items—seven functional and three attitudinal. Functional items assess eating speed, difficulty chewing solid food, food restrictions, difficulty chewing due to loss of teeth, swallowing, and changes in food preparation. Attitudinal items assess the extent to which patients are bothered by changes in eating habits, teeth, and mouth dryness. Subjects responded to items on a 5-point ordinal scale, with questions assessing either severity (options ranging from "Not at all" to "Extremely") or frequency (options ranging from "Never" to "Always"). Adequate reliability and validity of this measure have previously been reported (Funk et al., 2003). Test-retest reliability of the entire measure and specifically the eating domain were very high (r=0.85 and r=0.84, respectively), as were measures of internal consistency (Cronbach's alpha=0.95 for the measure and 0.92 for the eating domain).

Primary Measures

Beck Depression Inventory (BDI; see Appendix B) (Beck, Rush, Shaw, & Emery, 1979). Symptoms of depression were measured using the BDI, a widely used and well-validated standardized self-report assessment of depression symptomatology (Beck, Steer, & Carbin, 1988). The BDI consists of 21 items which participants respond to on an ordinal scale (0–3) regarding the intensity of signs and symptoms of depression. The BDI provides a continuous measurement of symptomatology by providing a total score (0–63). This measure has demonstrated high internal consistency, test-retest reliability, and concurrent validity in

psychiatric and non-psychiatric samples (Beck et al., 1988). Only one study has addressed the comparative accuracy of the BDI to other depression screening measures in HNC patients. Katz and colleagues (2004) reported that the BDI was highly accurate in identifying depression (area under the curve > 0.96) compared to a diagnostic clinical interview, and its receiver operating characteristic curves were not significantly different from other self-report measures. These results suggest that, as in other medically ill samples, the BDI appears to provide an accurate assessment of depression in HNC patients.

Given the overlap between depression symptoms and the present study's outcome of weight loss, BDI questions regarding change in appetite and change in weight were not included in the total BDI score used in primary analyses. Thus, the total BDI score used in primary analyses comprehensively reflected somatic and cognitive-affective symptoms of depression, with the exception of the two items related to change in appetite and weight. As a supplemental comparison analysis, parallel models were evaluated using only the cognitive-affective questions on the BDI, in place of the full BDI score minus weight-related items.

Weight change. Patients' height in inches and weight in pounds were measured at baseline and reassessed at each time point. These measurements were conducted by medical staff as part of the patients' clinic visits, and the values were extracted from the patients' medical records and entered into the OAP database. Additionally, these values were used to calculate BMI. For the present study, weight and BMI values corresponding to each study time point were extracted from the OAP database. Because net change in weight affects individuals to varying degrees based upon their body compositions, proportion of body weight lost is a more meaningful way to compare individuals than net weight loss. Thus, as in previous studies in this field, the present study conceptualized weight loss as overall percentage change in weight,

relative to diagnosis/baseline. The following formula was used to calculate each patient's total percentage weight lost at each time point:

$$\frac{(weight\ at\ diagnosis) - (weight\ at\ time\ point)}{(weight\ at\ diagnosis)}\ X\ 100$$

For example, if weight at baseline = 185 pounds and weight at 6-month follow-up = 160 pounds, baseline–6-month weight loss = 25 pounds (185-160 = 25) and percentage weight loss = 13.5% (25/185=0.135 X 100=13.5). If a negative value arose, this signified weight gain. To allow for examination of meaningful weight gain as a control variable in analyses, a categorical weight gain variable was created to identify which patients gained > 5% of their initial body weight by the 6-month time point.

Data Analytic Strategy

Descriptive analyses. Descriptive statistics were conducted in IBM SPSS Statistics for Windows (version 21.0) to evaluate the sample's clinical and demographic characteristics and assess the average amounts of weight loss and depressive symptoms at each time point. Chi-square and independent sample *t* tests were conducted to assess for significant differences between OAP patients who met inclusion criteria for the present study (i.e., those who had valid measurements of weight and depression symptoms at baseline and at least one additional time point) and OAP patients who did not meet inclusion criteria. Standardized residuals (*z*-scores) were evaluated to investigate significant differences.

Bivariate Pearson correlations were conducted as preliminary analyses of the associations between demographic and clinical variables and percentage weight loss and depressive symptoms at the 6-month time point. First, categorical control variables were dichotomized (i.e., dummy coded) to allow for direct group comparisons (e.g., whether the results differed

significantly for patients who received *single-* versus *multi-modality* treatment). Variables that were correlated with both outcomes of interest at the intercept time point (i.e., correlated with percentage weight loss at the 6-month assessment and depressive symptoms at the 6-month assessment) at a significance level of $p < .01$ were considered potential control variables and were retained for further analysis. The following variables were evaluated with data collected at baseline: sex, age, BMI, cancer site, cancer stage (*advanced* (stage III-IV) or *early* (stage I-II)), cancer status at diagnosis (*recurrence* or *non-recurrence*), treatment modality (three separate direct comparisons: *single-* or *multi-modality* treatment; *radiation* or *non-radiation*; *radiation and chemotherapy* or *other*), years of tobacco use, previous tobacco use (*never* or *ever*), years of alcohol use, and alcohol abuse (MAST). The following variables were evaluated with data collected at the intercept time point (6-month follow-up): BMI, weight gain (*gained $\geq$ 5% of initial body weight by 6-month follow-up* or *did not gain $\geq$ 5% of initial body weight by 6-month follow-up*), current use of a gastric feeding tube (*yes* or *no*), current dietary status (*NPO* or *not-NPO*), current tobacco use (*yes* or *no*), pain level, and eating-related HRQOL (HNCI-eating subscale).

Growth curve analyses. Comprehensive analyses were conducted using GCM techniques (Raudenbush & Bryk, 2002) with the HLM 7 software (Raudenbush, Bryk, & Congdon, 2004).

Model development. In GCM, a simultaneous, two-stage process of analysis is conducted. Level 1 determines whether the variable demonstrates significant change over time. At Level 1, a growth curve is modeled for each individual participant (Bryk & Raudenbush, 1987). This growth curve or trajectory of within-person change is estimated based upon two parameters: intercept (the level of the variable at a certain point in time) and slope (the rate of

change in the variable over time). In the present study, time was modeled as months since the 6-month assessment (based on unique dates of completion for each participant), thus the intercept represents scores at each participant's unique 6-month assessment. GCM analyzes whether, on average, intercepts and slopes differ significantly from zero and whether there is significant variability in parameter estimates across participants (e.g., whether participants vary in their rates of change over time). At Level 2, time-invariant participant characteristics or experiences are tested as predictors of between-person differences in Level 1 parameters (Bryk & Raudenbush, 1987) (DeLucia & Pitts, 2006). Specifically, these characteristics are incorporated as predictors of individual variation in the intercept (i.e., levels of the outcome variable at the 6-month assessment) and slope (i.e., rates of change in the outcome variable over time). In GCM, the coefficients represent the degree of association between two variables and are functionally comparable to unstandardized regression coefficients. Because the effects are estimated simultaneously, effects on one parameter are controlled for when estimating effects on other parameters.

Preliminary steps to address Aims #1 and #2: Baseline model specification. First, baseline models of change are tested to evaluate whether (a) total percentage weight loss and (b) depressive symptoms demonstrate significant systematic change over time, and to identify the nature of that change (e.g., linear versus curvilinear). The observed means for total percentage weight loss and depressive symptoms at each time point were used to develop hypotheses about expected patterns of change. Based on the observed means, it was expected that percentage weight loss would change in a negative curvilinear pattern over time (on average), such that levels increase, peak around month 6, and then decrease (i.e., inverted U-shape). To evaluate this, a quadratic model is initially tested and its fit is compared to the fit of a linear model. If the

addition of the quadratic parameter improves the fit of the model, the quadratic model is retained; however, if the fit is not improved, a more parsimonious, linear model is adopted for subsequent analyses. The HLM hypothesis testing function is used to determine the best fitting model for the data. Additionally, I predicted significant between-subject variability in rates of curvilinear change and levels at 6 months, which is necessary to test Level 2 predictors of these Level 1 parameters.

Based on the observed means, I expected that depressive symptoms would *not* demonstrate a systematic pattern of change over time but, instead, would wax and wane or fluctuate over time. This is consistent with a typical course of depression, which is characterized by discrete episodes, followed by periods of remission. To evaluate this, an intercept only model is initially tested. To account for the possibility of systematic change over time, the fit of the intercept only model is compared to the fit of a linear model including time as a Level 1 predictor using the HLM hypothesis testing function.

CHAPTER 7: RESULTS

Descriptive Analyses

The sample demographics are reported in Table 1. Consistent with epidemiological data on HNC patients (Cooper et al., 2009), participants were primarily Caucasian males that were approximately 60 years old (*SD* = 12.3) at time of diagnosis and were either using tobacco at time of diagnosis (27.6%) or had a history of tobacco use (47.7%). Additionally, of patients who filled out the MAST pretreatment, 21.4% were classified as problem drinkers and 10.3% were classified as possible alcoholics. Oral cavity cancers comprised the largest single group (41.3% of cases), although a range of HNC sites were represented. Over half of participants presented with advanced stage HNC (55.3% stage III–IV), and cases were most commonly treated either exclusively through surgery or through a combination of surgery and radiotherapy (36.5% and 25.9%, respectively). Eleven percent enrolled in the OAP with a recurrence of a primary tumor that was previously treated elsewhere. Correlational analyses identified the following variables as potential control variables (*p*s < .01): cancer stage (*advanced* (stage III-IV) or *early* (stage I-II)), treatment modality (*single* or *multimodal* comparison), weight gain (*gained* $\geq$ *5% of initial body weight by 6-month follow-up* or *did not gain* $\geq$ *5% of initial body weight by 6-month follow-up*), eating-related HRQOL, and pain level.

Chi-square and independent sample *t* tests comparing OAP patients who met study inclusion criteria to OAP patients who did not indicated that the groups were not significantly different in terms of age, race, marital status, cancer stage, recurrence status at diagnosis, alcohol use or abuse at diagnosis, or use of a gastric tube at diagnosis. Significant group differences were found, however, for sex (χ^2 (1) = 7.95, p = .005), cancer site (χ^2 (5) = 26.63, p < .001), and tobacco use at diagnosis (χ^2 (2) = 30.26, p < .001). Among patients who met inclusion criteria,

significantly more than expected were female ($z = 2.0$, $p < .01$), had oral cavity cancer ($z = 3.2$, $p < .01$), and had never used tobacco ($z = 2.5$, $p < .05$), and significantly fewer than expected had laryngeal cancer ($z = -2.6$, $p < .01$) and were using tobacco at diagnosis ($z = -3.7$, $p < .001$). Descriptive statistics for average levels of depressive symptoms and percentage weight loss across the first 12 months following HNC diagnosis are reported in Table 2. Although average level of depressive symptoms remained fairly consistent across time, the highest level was observed at the 6-month follow-up ($M = 7.31$, $SD = 7.27$), which is consistent with HNC literature regarding trajectories of depression (de Graeff et al., 1999; de Leeuw et al., 2000). After the 6-month assessment, patients' depression scores declined to below baseline levels, on average. Average percentage weight loss, however, peaked at the 9-month follow-up ($M = 6.41$, $SD = 9.81$). Given the variability in previously reported trajectories of weight loss following HNC, the timing of this peak is consistent with some reports and somewhat later than others (Brown et al., 2014; Couch et al., 2014; Silander et al., 2013). Although the sample's average weight loss at the 9-month follow-up was 6.41%, it is notable that 39.3% of patients with weight data at this time point had lost at least 10% of their body weight since diagnosis. An additional 13.4% lost 5–9.9% and 20.4% lost weight totaling less than 5% of baseline body weight, totaling 73% of patients having lost some percentage of weight since diagnosis. This descriptive data provides additional information about the prevalence and severity of post-diagnosis weight loss in this sample.

Primary Analyses: Evaluating Temporal Precedence Aims #1 and #2

Baseline model specification: Percentage weight loss. A quadratic model of percentage weight loss was initially tested:

Level 1:

$$Y_{ij}\ (\text{percentage weight loss}) = \beta_{0j}\ (\text{intercept}) + \beta_{1j}\ (\text{time}) + \beta_{2j}\ (\text{time}^2) + r_{ij}\ (\text{error})$$

Table 2

Descriptive Statistics for Depressive Symptoms and Percentage Weight Loss

Variable	*M* (*SD*)	n	%
Depressive symptoms[a]			
Baseline/Pretreatment	7.14 (6.41)	564	
3 months	6.92 (6.34)	372	
6 months	7.31 (7.27)	357	
9 months	6.37 (6.52)	311	
12 months	6.31 (6.88)	367	
Percentage Weight Loss[b]			
3 months	4.74 (6.93)	434	
6 months	6.09 (9.81)	366	
9 months	6.41 (10.64)	325	
12 months	5.44 (11.81)	364	
Percentage Weight Loss Categorization at 9 Months[b]		251	
Lost ≥ 10%		123	39.3
Lost 5–9.9%		42	13.4
Lost < 5%		64	20.4
Gained < 5%		56	17.9
Gained ≥ 5%		28	8.9

[a] Full scale BDI minus two weight-related items

[b] Relative to baseline, calculated for each patient using the following formula:

$$\frac{(weight\ at\ diagnosis) - (weight\ at\ time\ point)}{(weight\ at\ diagnosis)}\ X\ 100$$

Level 2:

β_{0j} (intercept) = $\gamma_{00} + \mu_{0j}$
β_{1j} (time) = $\gamma_{10} + \mu_{1j}$
β_{2j} (time^2) = $\gamma_{20} + \mu_{2j}$

where Y_{ij} represents levels of percentage weight loss at time i for person j, β_{0j} is the intercept for person j (modeled as levels at 6 months), slope coefficient β_{1j} is the linear growth rate for person j at time i, slope coefficient β_{2j} is the curvature or quadratic acceleration in growth over time, and

r_{ij} is the residual variance in repeated measures for person j (assumed to be independent and normally distributed).

As predicted, percentage weight loss followed a negative curvilinear pattern (inverted U-shape; t (562) = -4.12, $p < .001$) across the first year after HNC diagnosis, on average (see Figure 1). Additionally, there was significant between-subject variability in rates of curvilinear change (β_{2j}), χ^2 (320) = 569.57, $p < .001$, and levels of weight loss at 6 months (β_{0j}), χ^2 (320) = 6277.64, $p < .001$, which are necessary to test Level 2 predictors of these Level 1 parameters. Thus, percentage weight loss demonstrated systematic negative quadratic change across the first year of treatment, on average, for the sample and variability existed, with some patients experiencing greater curvilinear change than others. A quadratic model was a better fit to the data than a linear model, χ^2 (3) = 148.72, $p < .001$.

Baseline model specification: Depressive symptoms. The following intercept only model of depressive symptoms was initially tested:

Level 1:

Y_{ij} (depressive symptoms) = β_{0j} (intercept) + r_{ij} (error)

Level 2:

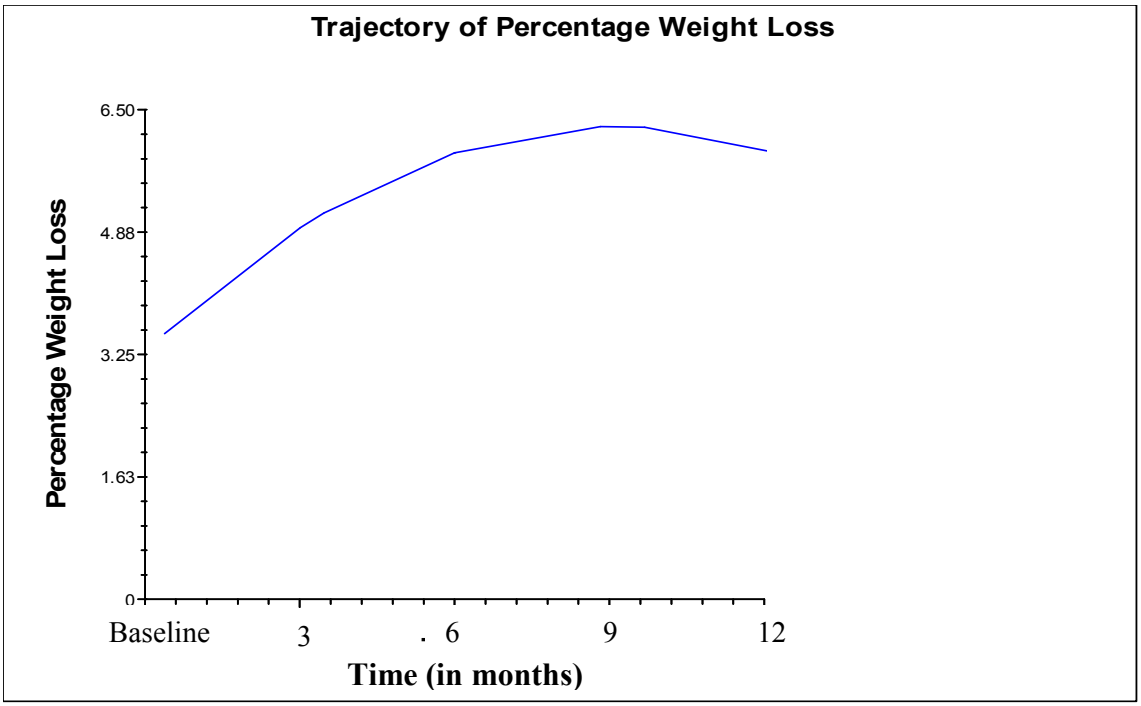
β_{0j} (intercept) = $\gamma_{00} + \mu_{0j}$

where Y_{ij} represents levels of depressive symptoms at time i for person j, β_{0j} is the intercept for person j (overall levels of depressive symptoms across time), and r_{ij} is the residual variance in repeated measures for person j. (Note that time is not included in the model.)

The prediction that this intercept only model, depicting depression waxing and waning over time in a non-systematic way, would be the best-fitting model was not supported. Rather, a linear model was a better fit to the data, χ^2 (2) = 23.59, $p < .001$. This model included time at both Level 1 and Level 2:

Figure 1

Average Curvilinear Pattern of Change in Percentage Weight Loss Across the First 12 Months Following HNC Diagnosis



Level 1:

Y_{ij} (depressive symptoms) = β_{0j} (intercept) + β_{1j} (time) + r_{ij} (error)

Level 2:

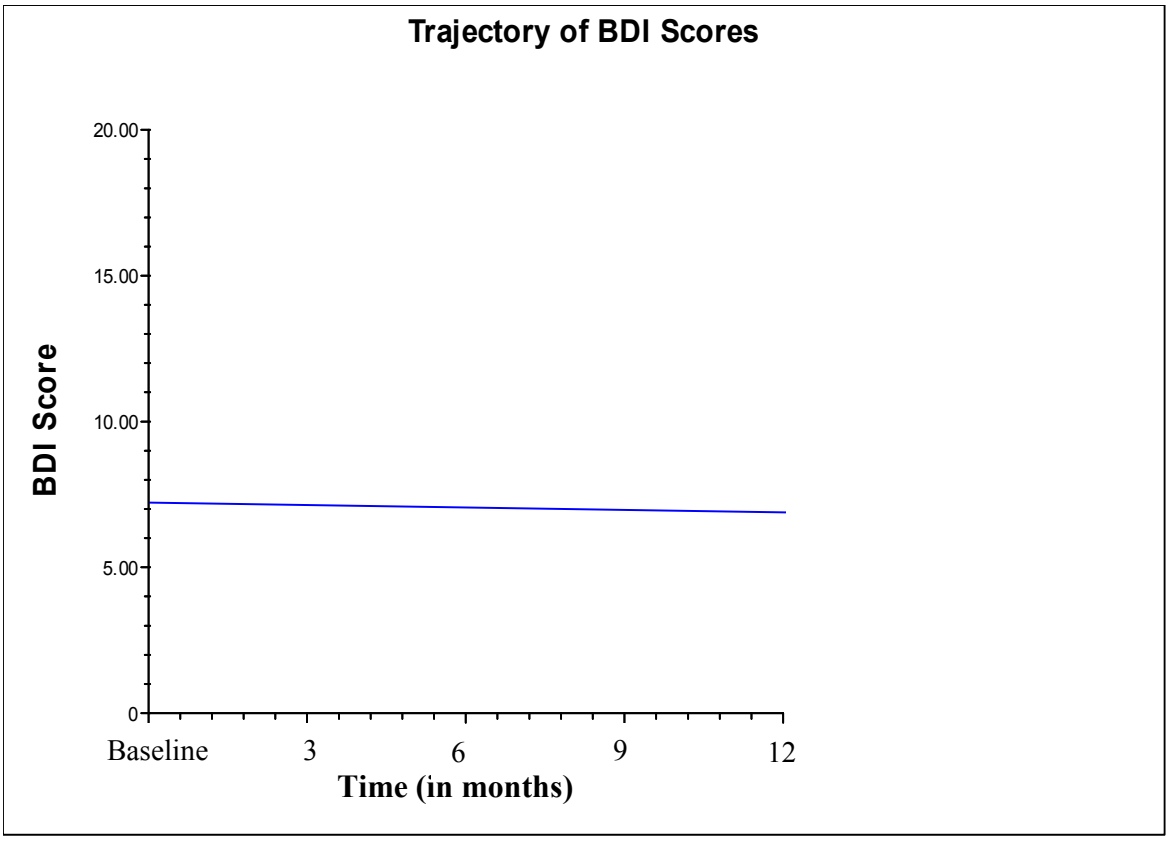
β_{0j} (intercept) = $\gamma_{00} + \mu_{0j}$
β_{1j} (time) = $\gamma_{10} + \mu_{1j}$

On average, depressive symptoms were relatively stable across the first year after HNC diagnosis, t (562) = -1.35, p = .18 (see Figure 2). However, consistent with predictions, there was significant between-subject variability in rates of change in depression across time (β_{1j}), χ^2 (561) = 791.24, $p < .001$. Thus, although depressive symptoms were relatively stable on average for the sample, they did change at different rates (perhaps increasing or decreasing significantly

over time) for some patients. Although there was evidence that including a quadratic parameter β_{2j} improved the fit of the model, χ^2 (3) = 26.63, $p < .001$, there was not significant between-subject variability in rates of quadratic change, χ^2 (438) = 459.98, $p = .23$. Therefore, the linear model was retained.

Figure 2

Average Linear Pattern of Change in Depressive Symptoms Over the First 12 Months Following HNC Diagnosis



Aim #1: Do baseline depressive symptoms predict weight loss outcomes? To evaluate Study Aim #1, I assessed whether depressive symptoms at baseline were associated with (a) total

percentage weight loss at 6 months (β_{0j}), and (b) rates of curvilinear change in percentage weight loss over time (β_{2j}). This entailed testing the following model, in which depressive symptoms at baseline were incorporated at Level 2 as a predictor of Level 1 parameters:

Level 1:

Y_{ij} (percentage weight loss) = β_{0j} (intercept) + β_{1j} (time) + β_{2j} (time^2) + r_{ij} (error)

Level 2:

β_{0j} (intercept) = γ_{00} + $\mathbf{\gamma_{01}}$ **(baseline depression symptoms)** + μ_{0j}
β_{1j} (time) = γ_{10} + γ_{11} (baseline depression symptoms) + μ_{1j}
β_{2j} (time^2) = γ_{20} + $\mathbf{\gamma_{21}}$ **(baseline depression symptoms)** + μ_{2j}

I expected patients with higher depression scores at baseline to experience (a) higher total percentage of weight loss at 6 months (a significant positive γ_{01} coefficient) and (b) greater negative curvilinear change in percentage weight loss (a significant negative γ_{21} coefficient). However, baseline depressive symptoms were neither associated with (a) total percentage weight loss at 6 months (β_{0j}), t (561) = -1.50, p = .13, nor with (b) rates of curvilinear change in percentage weight loss over time (β_{2j}), t (561) = 1.38, p = .17. Thus, baseline level of depressive symptoms did not differentiate either the severity or trajectory of percentage weight loss. Given that no relationship was found, Sub-Aim #1.1 investigating the unique predictive utility of baseline depressive symptoms on weight loss, beyond the effects of control variables, was not explored.

Aim #2: Does early weight loss predict depressive symptoms? To evaluate Aim #2, I assessed whether early weight loss (between baseline and 3-month follow-up) was associated with (a) overall levels of depression symptoms at 6 months (β_{0j}) and (b) linear change in depression symptoms over time (β_{1j}). This entailed testing the following model, in which

percentage weight loss between baseline and the 3-month follow-up was incorporated at Level 2 as a predictor of Level 1 parameters:

Level 1:

Y_{ij} (depressive symptoms) = β_{0j} (intercept) + β_{1j} (time) + r_{ij} (error)

Level 2:

β_{0j} (intercept) = γ_{00} + $\boldsymbol{\gamma_{01}}$ **(early percentage weight loss)** + μ_{0j}
β_{1j} (time) = γ_{10} + $\boldsymbol{\gamma_{11}}$ **(early percentage weight loss)** + μ_{1j}

A significant positive γ_{01} coefficient would suggest that patients with higher initial percentage weight loss have higher overall levels of depression symptoms at 6 months and a significant positive γ_{11} coefficient would indicate that these patients experience greater linear change in depressive symptoms.

In this analysis, 130 subjects were lost due to missing weight data at the 3-month follow-up, which was required to calculate percentage weight loss since baseline. Degree of early percentage weight loss was neither associated with (a) overall level of depressive symptoms at 6 months (β_{0j}), t (432) = 0.24, p = .81, nor with (b) rates of linear change in depressive symptoms over time (β_{1j}), t (432) = 1.31, p = .19. Thus, early weight loss did not differentiate the severity or pattern of depressive symptoms. Given that no relationship was found, Sub-Aim #2.1 investigating the unique predictive utility of early weight loss on depressive symptoms, beyond the effects of control variables, was not explored.

Evaluating cognitive-affective depressive symptoms. For comparison, parallel models were evaluated using only the cognitive-affective questions on the BDI, in place of the full BDI score minus weight-related items.

Baseline model specification. The baseline model specification for cognitive-affective depressive symptoms exactly mirrored that of the comprehensive depressive symptom score. A

linear model proved to be the best fit to the data, χ^2 (2) = 17.48, $p < .001$. Likewise, although cognitive-affective depressive symptoms were relatively stable on average for the sample, t (562) = -0.12, $p = .90$, they did change at different rates over time for some patients, χ^2 (562) = 850.67, $p < .001$. Although the addition of the quadratic parameter β_{2j} further improved the fit over the linear model, χ^2 (3) = 27.94, $p < .001$, the lack of significant between-subject variability in rates of quadratic change, χ^2 (438) = 469.13, $p = .15$, precluded further evaluation of this model and a linear model was retained. Thus, the nature of change in cognitive-affective depressive symptoms across time was entirely consistent with that of the comprehensive depressive symptom score.

Aim #1 Parallel: Do baseline cognitive-affective depressive symptoms predict weight loss outcomes? The parallel analysis of Aim #1 examined whether baseline cognitive-affective symptoms predicted weight loss outcomes. The pattern of results did not differ when cognitive-affective symptoms of depression were used in place of the comprehensive depression measure. Baseline cognitive-affective symptoms of depression were neither associated with (a) total percentage weight loss at 6 months (β_{0j}), t (561) = -1.48, $p = .14$, nor with (b) rates of curvilinear change in percentage weight loss over time (β_{2j}), t (561) = 0.95, $p = .34$.

Aim #2 Parallel: Does early weight loss predict cognitive-affective depressive symptoms? The parallel analysis of Aim #2 examined whether percentage weight loss between baseline and the 3-month follow-up was associated with cognitive-affective depressive symptoms across time. Once again, 130 subjects were lost due to missing weight data at the 3-month follow-up. The pattern of results did not differ when cognitive-affective symptoms of depression were used in place of the comprehensive depression measure. Degree of early percentage weight loss was neither associated with (a) overall levels of cognitive-affective

depressive symptoms at 6 months (β_{0j}), t (432) = -0.63, p = .53, nor with (b) rates of linear change in cognitive-affective depressive symptoms over time (β_{1j}), t (432) = 0.51, p = .61. Thus, early weight loss did not differentiate the severity or pattern of cognitive-affective depressive symptoms.

In sum, cognitive-affective symptoms of depression demonstrated the same pattern of change over time as the full depression measure minus weight-related items, as well as the same non-significant relationships with percentage weight loss in temporal precedence models.

Supplementary GCM Analyses: Evaluating Concurrent Covariation

Given the lack of support for the temporal precedence models addressed by Aims #1 and #2, and after discussing supplementary analytic strategies with my statistical consultant, I had additional interest in exploring whether the association between depressive symptoms and percentage weight loss was better characterized by concurrent covariation. As such, a third aim was added:

Aim #3: To evaluate whether a reciprocal concurrent covariation effect existed, such that *changes in* depressive symptoms across time influenced *concurrent changes in* percentage weight loss, and vice versa.

To evaluate this aim, time-varying covariation models were tested to examine the extent to which depressive symptoms and percentage weight loss changed in concert over time. Notably, these analyses examined whether changes in one variable predicted *concurrent* changes in the other, and did not examine whether changes in one variable predicted *subsequent* changes in the other. Thus, they examined immediate (rather than delayed) effects of one variable on another over the course of time, controlling for the overall trajectory of the dependent variable. The covariation analyses evaluated whether change in one variable predicted concurrent change in

the dependent variable, above and beyond change in the dependent variable occurring as a function of the passage of time. Although covariation models lack evaluation of temporal precedence, there is actually an inherent degree of directional prediction, given that the models control for the impact of time on the dependent variable. Therefore, examination of two covariation models was required in order to examine the covariation association while separately controlling for the impact of the passage of time on percentage weight loss and depression.

Covariation Model A: Examined whether change in depressive symptoms resulted in deviations from the average trajectory of percentage weight loss.

Covariation Model B: Examined whether change in percentage weight loss resulted in deviations from the average trajectory of depressive symptoms.

Covariation Methods. To examine Covariation Model A, I assessed whether changes in depressive symptoms over time were associated with concurrent changes in percentage weight loss, beyond changes in weight attributed to the passage of time. This entailed testing the following model, in which depressive symptoms were entered at Level 1 as a time-varying variable:

Level 1:

Y_{ij} (percentage weight loss) = β_{0j} (intercept) + β_{1j} (depressive symptoms) + β_{2j} (time) + β_{3j} (time^2) + r_{ij} (error)

Level 2:

β_{0j} (intercept) = $\gamma_{00} + \mu_{0j}$
β_{1j} (depressive symptoms) = γ_{10}
β_{2j} (time) = $\gamma_{20} + \mu_{2j}$
β_{3j} (time^2) = $\gamma_{30} + \mu_{3j}$

Covariation Model B examined covariation between percentage weight loss and changes in depressive symptoms, controlling for the impact of time on depressive symptoms. Percentage weight loss was entered as a time-varying variable at Level 1:

Level 1:

Y_{ij} (depressive symptoms) = β_{0j} (intercept) + β_{1j} (percentage weight loss) + β_{2j} (time) + r_{ij} (error)

Level 2:

β_{0j} (intercept) = $\gamma_{00} + \mu_{0j}$
β_{1j} (percentage weight loss) = $\gamma_{10} + \mu_{1j}$
β_{2j} (time) = $\gamma_{20} + \mu_{2j}$

Significance of Covariation Model A, but not Covariation Model B, would suggest that depressive symptoms influenced concurrent changes in percentage weight loss, but not vice versa. Significance of Covariation Model B, but not Covariation Model A, would suggest that percentage weight loss influenced concurrent changes in depressive symptoms, but not vice versa. Significance of both models would suggest a reciprocal/bidirectional relationship, such that changes in either variable influenced concurrent changes in the other, beyond the changes already occurring in the variables due to the passage of time.

Covariation Results. In Covariation Model A, changes in depressive symptoms were associated with concurrent deviations from average trajectories of percentage weight loss, t (1148) = 2.05, p = .041 (see Table 3 for detailed model results). To the extent that depressive symptoms increased on a monthly basis, patients lost incrementally more weight than was lost due to the passage of time. Specifically, a one unit monthly increase in depressive symptoms was associated with a 0.07 increase in percentage weight loss during the same month, above and beyond the change in percentage weight loss occurring due to the passage of time. To get

Covariation Model A to converge, depressive symptoms were modeled as a fixed effect (i.e., the association between changes in depressive symptoms and changes in weight was modeled as the same across the sample). All other parameters were modeled as random effects.

In Covariation Model B, changes in percentage weight loss were associated with concurrent deviations from average trajectories of depressive symptoms, t (556) = 2.44, p = .015 (see Table 3 for detailed model results). To the extent that percentage weight loss increased on a monthly basis, patients experienced a greater increase in depressive symptoms than that which occurred due to the passage of time. Specifically, a one unit monthly increase in percentage weight loss was associated with a 0.06 increase in depression scores during the same month, above and beyond the change in depressive symptoms occurring due to the passage of time. Although all parameters were modeled as random effects, the lack of significant between-subject variability in rates of change in percentage weight loss, χ^2 (243) = 254.52, p = .29, indicated that the association was robust across the sample (i.e., it did not vary across patients). This indicates that the overall association between percentage weight loss and depressive symptoms was the same across the sample and did not vary in strength or direction as a function of disease- or patient-related factors.

Taken together, the results indicate that changes depressive symptoms and percentage weight loss covary over time. More specifically, the longitudinal association between these variables appears to be reciprocal in nature—changes in either variable across time influenced concurrent changes in the other. In other words, to the extent that one of these variables increased on a monthly basis across time so did the other, incrementally more than it would have changed due to the passage of time.

Table 3

Results of Covariation Analyses

Covariation Model A	Coefficient	*SE*	*t*	*df*	*p*
β_{0j} (Intercept)	5.86	0.42	14.06	556	<.001
β_{1j} (Depressive Symptoms)	0.07	0.03	2.05	1148	.041
β_{2j} (Time)	0.22	0.06	3.49	556	<.001
β_{3j} (Time^2)	-0.04	0.01	-3.76	556	<.001
Pain[a] Included					
β_{1j} (Depressive Symptoms)	0.02	0.04	0.42	665	0.673
Eating HRQOL[a] Included					
β_{1j} (Depressive Symptoms)	-0.02	0.04	-0.38	690	0.707
Covariation Model B	Coefficient	*SE*	*t*	*df*	*p*
β_{0j} (Intercept)	6.95	0.26	26.43	556	<.001
β_{1j} (Percentage Weight Loss)	0.06	0.02	2.44	556	.015
β_{2j} (Time)	-0.09	0.03	-3.15	556	.002
Pain[a] Included					
β_{1j} (Percentage Weight Loss)	0.03	0.03	0.97	322	.334
Eating HRQOL[a] Included					
β_{1j} (percentage Weight Loss)	-0.02	0.03	-0.67	337	.506

Note. Covariation Model A demonstrated that changes in depressive symptoms were associated with concurrent changes in percentage weight loss, beyond changes in weight attributed to the passage of time. Covariation Model B demonstrated that changes in percentage weight loss were associated with concurrent changes in depressive symptoms, beyond changes in depressive symptoms attributed to the passage of time.

[a] Measured at the 6-month assessment.

Examining control variables: Methods. Just as the evaluation of the two covariation models (separately controlling for the effects of the passage of time on depressive symptoms and percentage weight loss, respectively) was required to interpret a reciprocal relationship, potential control variables of this reciprocal relationship required separate evaluation in each covariation model (i.e., A and B). For each potential control variable, I specified the exact same Level 1 model used to examine the covariation models and entered the potential control variable into the Level 2 equations as a predictor of the intercept and slope parameters. This approach comprehensively examined whether the overall trajectories (both the levels and rates of change) of depressive symptoms and percentage weight loss varied as a function of each control variable. As such, the following general model was specified for examining control variables of Covariation Model A:

Level 1:

Y_{ij} (percentage weight loss) = β_{0j} (intercept) + β_{1j} (depressive symptoms) + β_{2j} (time) + β_{3j} (time^2) + r_{ij} (error)

Level 2:

β_{0j} (intercept) = $\gamma_{00} + \gamma_{01}$ **(control variable)** + μ_{0j}
β_{1j} (depressive symptoms) = γ_{10}
β_{2j} (time) = $\gamma_{20} + \gamma_{21}$ **(control variable)** + μ_{2j}
β_{3j} (time^2) = $\gamma_{30} + \gamma_{31}$ **(control variable)** + μ_{3j}

For examining control variables of Covariation Model B, the following general model was specified:

Level 1:

Y_{ij} (depressive symptoms) = β_{0j} (intercept) + β_{2j} (percentage weight loss) + β_{1j} (time) + r_{ij} (error)

Level 2:

β_{0j} (intercept) = $\gamma_{00} + \gamma_{01}$ **(control variable)** + μ_{0j}
β_{1j} (percentage weight loss) = γ_{10} + μ_{1j}
β_{2j} (time) = $\gamma_{20} + \gamma_{21}$ **(control variable)** + μ_{2j}

Examining control variables: Results. The effect of changes in depressive symptoms on changes in percentage weight loss (Covariation Model A) was no longer significant when controlling for pain, t (665) = 0.42, p = 0.67, or eating-related HRQOL, t (690) = -0.38, p = 0.71. Likewise, the effect of changes in percentage weight loss on changes in depressive symptoms (Covariation Model B) was no longer significant when controlling for pain, t (322) = 0.97, p = 0.33, or eating-related HRQOL, t (337) = -0.67, p = 0.51. These results are reported with the primary covariation models in Table 3.

Thus, when patients' 6-month pain ratings and functional and attitudinal eating-related HRQOL ratings were included in the models, the concurrent effects of depressive symptoms on percentage weight loss and percentage weight loss on depressive symptoms were no longer significant. This suggests that the reciprocal relationship between depressive symptoms and percentage weight loss during the first year after HNC diagnosis occurs primarily through the shared association between these variables and 6-month pain and eating-related HRQOL. Both control variables (patient-reported pain and eating-related HRQOL at 6 months) were uniquely associated with the overall *level* (i.e., intercept) of percentage weight loss at 6 months (pain: t (321) = 2.79, p = 0.006; eating-related HRQOL: t (336) = -5.97, $p < 0.001$) and uniquely associated with the overall *level* (i.e., intercept) of depressive symptoms at 6 months (pain: t (321) = 5.10, $p < 0.001$; eating-related HRQOL: t (336) = -6.65, $p < 0.001$). Both control variables were also associated with the *rates of change* (i.e., slope) in percentage weight loss over time (pain: t (321) = -2.51, p = 0.01; eating-related HRQOL, t (336) = 1.83, p = 0.069,

marginal significance), but were not associated with the *rates of change* (i.e., slope) in depressive symptoms over time (pain: t (321) = -0.27, p = 0.79; eating-related HRQOL, t (336) = 1.11, p = 0.27).

Evaluating cognitive-affective symptoms of depression. For comparison, the covariation models were also examined using only the cognitive-affective symptoms of depression in place of the full BDI score minus weight-related items. In the parallel analyses to Covariation Model A, changes in cognitive-affective depressive symptoms were not associated with concurrent deviations from average trajectories of percentage weight loss, t (557) = 1.28, p = .20. The extent that cognitive-affective depressive symptoms increased on a monthly basis was not associated with concurrent changes in weight. Likewise, in the parallel analysis to Covariation Model B, changes in percentage weight loss were not associated with concurrent deviations from average trajectories of cognitive-affective depressive symptoms, t (557) = 1.56, p = .12. The extent that percentage weight loss changed on a monthly basis was not associated with concurrent changes in cognitive-affective depressive symptoms. Thus, the reciprocal covariation relationship between depressive symptoms and percentage weight loss was only present when the full BDI score (minus weight-related items) was used, and was not present when the cognitive-affective symptoms of depression were exclusively evaluated. This suggests that the comprehensive set of depression symptoms is reciprocally related to percentage weight loss, whereas the cognitive-affective symptoms alone do not covary with weight loss. Comprehensive assessment of depression through use of the full BDI in the primary analyses appears to have allowed for the strongest prediction of the relationship between depressive symptoms and weight loss.

CHAPTER 8: DISCUSSION

This investigation revealed nuanced findings regarding the association between depressive symptoms and UWL in HNC patients. The primary temporal precedence hypothesis that baseline depressive symptoms would predict both the severity and the pattern of UWL was not supported. The opposite temporal relationship, that of early UWL predicting the severity and course of depressive symptoms, also lacked support. The non-significance of these temporal precedence models prompted investigation into concurrent covariation models, which illustrate another type of longitudinal association between the variables.

These covariation analyses indicated that changes in depressive symptoms were associated with concurrent changes in UWL, and also that changes in UWL were associated with concurrent changes in depressive symptoms. To the extent that one of these variables increased on a month-to-month basis across the first year following HNC diagnosis, so did the other, beyond the changes already occurring due to the passage of time. Taken together, these results depicted an ongoing transactional interplay between depressive symptoms and weight loss over the first year after HNC diagnosis. Given the significance of both covariation models, the link between depressive symptoms and UWL appears to be reciprocal in nature. Across time, changes in either variable influenced concurrent deviations in the average trajectory of the other variable. Patients experiencing greater monthly increases in depressive symptoms experienced greater concurrent increases in weight loss and more instability in weight loss over time, and patients experiencing greater monthly increases in weight loss experienced greater concurrent increases in depressive symptoms and more instability in depressive symptoms over time. Moreover, this association was robust across the sample and did not vary in magnitude among subjects.

Notably, the reciprocal association was consistent across patients and did not vary in strength or direction across the sample, despite comprehensive inclusion of patients from various HNC sites, disease stages, and treatment modalities. This robust effect suggests the generalizability of the results to a diverse set of HNC patients. Furthermore, several patient, disease, and treatment characteristics that could theoretically be associated with depression and weight loss outcomes were evaluated as control variables. For the most part, their inclusion in analyses did not change the significance of the reciprocal covariation model (i.e., they did not explain the association between depression and percentage weight loss). This is particularly noteworthy for disease stage, cancer site, and treatment modality, which have been previously identified to be associated with depression and weight loss outcomes. Additionally, the fact that BMI did not explain the association between depression and weight loss may be particularly informative given that BMI can imply information about underlying inflammatory processes and given that obese HNC patients have reportedly had different patterns of weight loss and survival outcomes than non-obese patients (Karnell et al., 2014).

The reciprocal covariation relationship between depressive symptoms and UWL was, however, no longer significant when patient-reported pain or eating-related HRQOL were included as control variables. Rather than imply that depressive symptoms and UWL do not influence one another, these findings suggest that they primarily do so through shared associations with pain and eating-related HRQOL, and point to possible mechanisms through which depression and UWL influence one another. Patients reporting greater pain at 6 months experienced higher levels of depressive symptoms and percentage weight loss at 6 months, as well as greater instability in weight over time. Likewise, patients reporting poorer eating-related HRQOL at 6 months (i.e., those experiencing greater functional impairments in eating, chewing,

and swallowing, greater adjustments in meal preparation and eating techniques, and greater concern regarding changes in eating, teeth, and mouth dryness) experienced higher levels of depressive symptoms and percentage weight loss at 6 months, as well as greater instability in weight over time. Therefore, pain and eating-related HRQOL emerged as important variables clarifying the longitudinal relation between depressive symptoms and weight loss across the first year after HNC diagnosis.

In sum, baseline levels of depressive symptoms did not, themselves, predict a particular pattern of UWL, nor did early UWL predict a particular course of depressive symptomatology. Rather, changes in each of these variables across time influenced concurrent changes in the other variable, causing deviations from the average longitudinal trajectories of the variables. This pattern of results allows for comparative flexibility in timing and targets of intervention, as the results identified risk factors across time rather than at one particular point. Instead of identifying certain patients as likely to experience a particular outcome from the start based on a pretreatment characteristic, the study's results suggest a more immediate/contemporaneous effect of depressive symptoms on UWL and UWL on depressive symptoms.

Clinical Implications

Ongoing screening and treatment for both depression and UWL throughout the course of the first year after HNC diagnosis are warranted, and successful treatment for either would be expected to be associated with improvements in psychological and nutritional health alike. These results suggest that interventions that reduce depressive symptoms may also reduce weight loss, and also that patients who regain weight may experience a reduction in depressive symptoms.

It is noteworthy that many other risk factors for nutritional decline are related to non-modifiable aspects of the HNC tumor (e.g., stage, site) and its treatment. Thus, the identification of depressive symptoms as a risk factor for weight loss has important clinical implications, as it yields the possibility that depression treatment could influence both mental and physical health outcomes. Given that increases in weight loss also predicted increases in depressive symptoms, the importance of early nutritional intervention for nutritionally compromised patients is further supported by its potential impact on long-term mental health outcomes. Prophylactic nutritional intervention is already employed in some clinical settings (Beaver et al., 2001; Garg, Yoo, & Winquist, 2010; Silander et al., 2012), and expanded use of these measures could also improve depression outcomes. Furthermore, the results could alert medical providers to be particularly vigilant for development or increased severity of depressive symptoms in patients who experience increases in weight loss. The results further indicated that eating-related impairments and pain at the 6-month assessment may be mechanisms through which depressive symptoms and UWL influence one another. Thus, in addition to interventions that target depression and weight loss directly, improved functional eating abilities and pain management may also improve these important clinical outcomes.

Depression assessment. Although assessment for UWL is already integrated into most clinical oncology settings, iterative depression assessment is less likely to be. These results point to the predictive utility of a brief, patient-administered depression screening instrument to assist with early identification of at-risk patients. A screening tool could be used to identify possibly depressed patients who would benefit from a more formal diagnostic assessment. If such a screening measure is not already used, it could be implemented into routine clinical practice settings with minimal financial, employee, or time costs (Bottomley, 1998). Not only would

such iterative screening identify changes in mental health symptoms over time, but the present results further suggest that it could identify nutritionally at-risk patients.

Depression and HRQOL interventions. Unfortunately, research evaluating psychosocial interventions for depression in HNC patients is quite limited. A recent comprehensive Cochrane review identified four randomized controlled trials (RCTs) evaluating depression interventions in HNC patients (Semple et al., 2013). Three of these were nurse-led interventions and all consisted of individual psychoeducational and/or cognitive behavioral interventions. Two were quite brief (2–3 sessions) and the other two were more involved (6–11 sessions). This meta-analysis found no significant change in depression post-intervention or at follow-up (3–6 months post-intervention). The review also included three psychosocial interventions for improving QOL and psychological distress, more broadly. There was no compelling evidence that psychosocial interventions influenced global QOL or any functional QOL subscales (e.g., cognitive, physical, emotional, social, or role functioning). Overall, the review found inadequate evidence either favoring or contesting the effectiveness of psychosocial interventions in this population and noted that the small number of methodologically strong RCTs or quasi-RCTs limited the ability to make conclusive determinations. Unfortunately, none of the included studies evaluated nutritional or weight loss outcomes, and the studies measuring QOL did not use a HNC-specific or functional eating-specific QOL measure.

Since the publication of the Cochrane review, a few additional intervention studies have been published. Most notably, an RCT examining a psychosocial nurse-led intervention to help patients cope with the physical, psychological, and social consequences of HNC diagnosis and treatment found that depressive symptoms 12 months post-diagnosis were significantly lower for patients in the intervention group (-2.8 CES-D score, 95% confidence interval (CI): -5.2 to -0.3)

compared to those receiving treatment as usual (van der Meulen et al., 2013). Notably, the effect of the intervention on reducing depressive symptoms was even stronger (-5.2 CES-D score, 95% CI: -9.1 to -1.2) for patients with pretreatment elevated depression scores (CES-D $\geq$ 12). Depression symptoms remained significantly lower at 18 months post-diagnosis for patients who received the intervention and were lower, but no longer significantly so, at 24 months (van der Meulen et al., 2014). Importantly, this intervention was also associated with significant improvements in HRQOL (emotional functioning) at 12-, 18-, and 24-months post-diagnosis, and with decreased pain, fewer problems swallowing, and improved mouth-opening abilities at 12 and 18 months (van der Meulen et al., 2014). It is noteworthy that the intervention was associated with improvements in an array of emotional, physical, and functional symptoms, including depressive symptoms, pain, HRQOL, and successful swallowing and mouth opening—factors that the present study identified as important predictors of the trajectory of weight loss. The authors believed this was the first published RCT regarding interventions for improving HRQOL in HNC patients, and its methodology is also notable for including HNC-specific measures of functional HRQOL. Unfortunately, this intervention did not assess factors related to nutrition or weight loss, so it is unknown whether the improvements in depressive symptoms and eating-related functions were accompanied by reductions in UWL.

Other recently published HNC interventions include a nurse-led tailored information intervention for patients with advanced stage disease (D'Souza, Blouin, Zeitouni, Muller, & Allison, 2013) and a cognitive behavioral therapy (CBT) intervention for distressed, newly diagnosed patients (Kangas, Milross, Taylor, & Bryant, 2013). D'Souza and colleagues (2013) found that advanced-stage HNC patients who received tailored, interactive information through a multimedia presentation and one-on-one nurse interactions were less likely to be clinically

depressed three months later than patients who received routine information provision. Kangas and colleagues (2013) found that CBT and supportive counseling were similarly associated with reductions in depressive symptoms and improvements in QOL 6 and 12 months later; however, a greater proportion of patients in the CBT group no longer had clinically significant symptoms at 12 months. The predominance of nurse-led interventions is encouraging for ultimate feasibility and effectiveness. Interventions that can be integrated into routine care or existing medical appointments and led by a standing member of the treatment team, as with van der Muelen et al. (2013), have the greatest likelihood of dissemination, implementation, and reach.

Interestingly a broad array of HNC patients, not simply those that are initially distressed, may benefit from psychosocial interventions. Neither the van der Meulen et al. (2013, 2014) nor the D'Souza et al. (2013) intervention recruited patients based on elevated psychosocial symptom criteria. However, the treatment-as-usual control groups in these studies actually experienced *increases* in depressive symptoms, whereas patients in the intervention groups had declines in symptoms. These results suggest that the average HNC patient, regardless of initial psychosocial functioning, could benefit from such interventions, which may have a preventive effect. A psychosocial approach to depression prevention could be more effective than a pharmacological one, as prophylactic antidepressant medication use (40 mg of citalopram versus placebo) was not associated with significant differences in prevalence of HNC patients meeting clinical criteria for depression 12 or 16 weeks after medication initiation (Lydiatt, Denman, McNeilly, Puumula, & Burke, 2008). Thus, even in the absence of an elevated depression symptom score, psychosocial treatment warrants consideration as depression prevention for patients diagnosed with such a psychologically distressing illness.

Weight loss interventions. A meta-analysis of nutritional interventions in HNC patients undergoing radiotherapy evaluated dietary counseling, nutritional supplementation (e.g., protein-rich liquids such as Ensure), medication (megestrol acetate), and prophylactic enteral tube feeding interventions (Garg et al., 2010). When each approach was used in isolation, individualized, dietician-led counseling had the most beneficial impact on nutritional outcomes. Support was found for using nutritional supplementation or megestrol acetate as adjuncts to dietary counseling, but the authors noted the need for further methodologically strong research. In addition to their influence on nutritional outcomes, dietary counseling and use of supplements have been associated with improvements in QOL, with counseling having an apparently stronger influence on QOL three months post-radiation treatment (Ravasco et al., 2005).

Early use of enteral feeding tubes, in response to significant weight loss or presence of symptoms that impair oral nutrient intake, is typically associated with reductions in weight loss, malnutrition, and dehydration, as well as improvements in QOL (Beaver et al., 2001; Chasen & Bhargava, 2009). Prophylactic use of feeding tubes has also been implemented, and has been associated with less weight loss and malnutrition and better QOL than standard responsive nutritional interventions (Beaver et al., 2001; Garg et al., 2010; Silander et al., 2012). Consensus regarding the optimal method (i.e., nasogastric or percutaneous endoscopic gastrostomy) or timing (i.e., prophylactic or responsive) of tube feeding is lacking (Garg et al., 2010; Nugent, Lewis, & O'Sullivan, 2012).

Interdisciplinary interventions. The maximum clinical impact of interventions would likely occur in the context of an interdisciplinary treatment team. Integrating cross-discipline providers allows for more rapid access to nutritional and psychological interventions, extends the breadth of available treatments, and facilitates an enriched consideration of biopsychosocial

factors influencing important patient outcomes. A multifaceted approach could be particularly important for patients with especially complex presentations. For example, one HNC rehabilitation program enrolled patients with at least two high-risk issues (e.g., severe pain, significant weight loss, reduced functional ability) for treatment by an interdisciplinary team consisting of a physician, nurse, dietician, occupational therapist, physiotherapist, and, by referral, psychologist and social worker (Eades et al., 2013). These patients were nutritionally compromised upon enrollment in the program at an average of eight months posttreatment—74% were experiencing at least three nutritional problems (e.g., weight loss and functional abilities) and two-thirds had lost > 10% of their body weight in the previous six months—yet 78% gained or maintained body weight during the intervention. The rehabilitation program was associated with clinically meaningful improvements in anorexia, depression, distress ratings, and QOL (effect sizes 0.6–0.9). Approximately half of patients (45%) were referred to the psychologist or social worker for treatment, with an average of three appointments attended. This study did not evaluate associations between receipt of particular services and improvement in particular outcomes (e.g., did not evaluate changes in depression and distress specifically for patients who received mental health services). Thus, it is unknown whether the observed improvements represent direct effects, such as depression improving following treatment from a mental health provider, or crossover effects, such as depression improving following treatment from a dietician targeting weight gain.

Although clinically meaningful improvements in depression and/or QOL may be possible after only a few sessions of psychosocial intervention, it is important to consider that patients are less likely to follow through with external mental health referrals than with seeing a mental health provider who is integrated into the treatment team. In a descriptive analysis of the

perceived benefit of a psychologist who was integrated into a HNC treatment team, most patients and caregivers indicated that they would not have independently sought community psychological services had this psychologist not been integrated into their care, nor would they have been likely to follow through with an external mental health referral (Jesse et al., 2014). Although this psychologist evaluated all new HNC patients, those with a psychiatric history were particularly satisfied with the psychologist's ability to reduce distress and improve QOL. Importantly, fellow staff on the HNC treatment team described the widespread benefits of the integrated psychologist, including reducing health care provider stress, bridging patient–provider communication, and improving patient care.

Potential Mechanisms for the Reciprocal Effect

As previously mentioned, empirical investigations into mechanisms behind the associations between depression and nutritional outcomes have not been conducted. Patients with elevated depressive symptoms could experience reduced appetite, nutritional intake, and self-care behaviors, as well as anhedonia and decreased interest in social or eating-related activities, all of which could increase weight loss. Patients may respond to weight loss with depressed mood, catastrophic thinking, hopelessness, or poor body image, which could be reflected in increased depressive symptoms. The consequences of this increase in depressive symptoms (such as those stated above) could further influence weight loss, thus characterizing the ongoing reciprocal effect identified in this study.

The predictors or mechanisms of weight loss may vary based on distinct phases of the illness trajectory. For example, pretreatment weight loss is likely more related to tumor burden and tumor location, whereas weight loss during and following treatment is likely more associated with treatment-related side effects and impairment. Given that the present study exclusively

evaluated post-diagnosis weight loss, it is not surprising that the treatment sequelae of pain and eating-related HRQOL (encompassing functional impairments in eating, chewing, and swallowing, and the necessity of adjustments in meal preparation and eating techniques) were uniquely associated with overall trajectories of weight loss.

The shared associations between depressive symptoms, UWL, pain, and eating-related HRQOL suggest a cohesive conceptual framework for understanding these disease sequelae. The study's findings identified pain and eating-related HRQOL as possible mechanisms through which depression and UWL could influence one another. Patients with greater vulnerabilities for developing depression may also be prone to subjectively experiencing higher levels of pain, which could contribute to weight loss through an association between pain and nausea, fatigue, or appetite loss. Similarly, patients who develop depression may be more likely to evaluate their functional eating impairments more negatively, which could contribute to weight loss through changes in eating practices.

Pain, HRQOL, and depressive symptoms have been associated with one another in previous analyses of HNC patients. Depressive symptoms were associated with pain levels at posttreatment (Scharpf, Karnell, Christensen, & Funk, 2009; van der Meulen et al., 2013) and at one-year post-diagnosis (Shuman et al., 2012; van der Meulen et al., 2013), and changes in depressive symptoms across the first year after diagnosis were associated with changes in pain during that same time (van der Meulen et al., 2013). Additionally, posttreatment pain was associated with poorer physical and mental QOL (Scharpf et al., 2009), and one-year pain was one of the strongest independent predictors of long-term HRQOL, such that it was a better predictor of 5-year HRQOL than disease stage, site, or age (Funk et al., 2012). As previously reviewed, the associations between depressive symptoms and general and HNC-specific HRQOL

have been documented cross-sectionally and prospectively, and the overall courses of depression and HRQOL following diagnosis tend to parallel one another (Howren et al., 2013). However, most of these studies measured general HRQOL, as opposed to the eating-specific HRQOL measurement used in the present study that primarily captures functional eating abilities. Additionally, pain and depression often overlap in their symptom presentations—for example, pain is often associated with poor sleep quality (Shuman et al., 2012), fatigue, appetite loss, hopelessness, and irritability.

Finally, various neuroendocrine pathways could be contributing to the effects. A recently published study evaluated associations between depression, weight loss, and the appetite hormones leptin and ghrelin in HNC patients (Ozsoy, Besirli, Unal, Abdulrezzak, & Orhan, 2015). This study found that depression was associated with aggravated weight loss and lower leptin levels; no differences in levels of ghrelin were found. The authors believe this offers support that leptin, which is typically positively associated with body fat, may be a mechanism for depression–weight loss associations. Additionally, depression and nutritional impairment in cancer patients could share a common etiology associated with elevated levels of inflammatory cytokines. Tumor-induced release of cytokines may influence both mood and weight loss by influencing neuroendocrine pathways (Illman et al., 2005). These elevations in inflammatory cytokines and impairments in leptin–ghrelin functioning have been associated with depression and with symptoms of cancer cachexia, which represents a more multifaceted symptom profile than solely weight loss or treatable nutritional deterioration (Illman et al., 2005). Thus, the inflammatory cytokine and appetite hormone explanations may entail a more complex array of cachectic symptoms than merely the association between non-cachectic weight loss and depression. Furthermore, the hormones cortisol, adrenocorticotropic hormone, epinephrine, and

norepinephrine have been recognized as a collective mechanism for the common symptom cluster of pain, depression, and fatigue in cancer patients (Thornton, Andersen, & Blakely, 2010). This finding is particularly interesting given the present study's identification of pain as a control variable for the relationship between depressive symptoms and UWL.

Limitations

Conducting an analysis of an ongoing longitudinal cohort of patients presented both opportunities and limitations. Although the OAP database is a comprehensive and rich data source, the present analyses were limited to variables that were already being routinely collected. This led to utilization of percentage weight loss as a proxy measure of nutritional status. UWL is considered to be the best independent measurement of nutritional depletion in HNC patients and has demonstrated superior sensitivity and specificity compared to other nutritional indicators (Brown et al., 2014; Ravasco, Monteiro-Grillo, Vidal, et al., 2003). Additionally, it is a variable that is already routinely collected in clinical oncology settings, thus the potential translation of research findings employing this measurement into implementation is strong. Nonetheless, combining UWL with additional nutritional markers may have strengthened conclusions.

As in previous research investigating UWL in cancer patients, the present study was inherently limited by an inability to incorporate prediagnosis weight loss. The first recorded weight value occurred at the pretreatment (baseline) assessment period, yet it is common for HNC patients to lose weight prior to this point. In fact, recent weight loss may even be a symptomatic complaint that spurs patients to seek the medical evaluation that ultimately results in cancer diagnosis. Thus, this study does not capture the full amount of weight loss that patients experience. It more closely illustrates weight loss associated with or exacerbated by treatment and treatment-induced impairments, rather than weight loss associated with the tumor burden or

location. Because predictors and mechanisms of UWL may vary at distinct illness phases, it is important to note that the study's findings should not be assumed to generalize to pretreatment UWL. Other studies have addressed this challenge by using patient-estimated prediagnosis weight loss in analyses. This approach, which has questionable accuracy, was not an option because the present study analyzed an existing data set. Theoretically, patient-reported UWL would be assessed upon presentation in the oncology clinic and thus documented in patients' initial clinic notes. However, investigation of OAP participants' electronic medical records indicated that diagnosing providers were inconsistent in whether they noted the presence and/or the degree of UWL in patients' charts. The large degree of inconsistency in documenting patient-reported UWL precluded utilizing this medical chart information in analyses.

Similarly, the study is limited in its inability to know the level of prediagnosis depressive symptoms. Although the largest increase in depressive symptoms has been observed between pretreatment and the conclusion of treatment (Chen et al., 2009; Hammerlid et al., 1999; Kelly et al., 2007), theoretically an even larger change in symptoms could occur immediately after HNC diagnosis. The degree of change from prediagnosis levels of depression to those at the baseline/pretreatment assessment may be differentially meaningful for UWL, yet are not captured by this or other studies. Additionally, patients who have persistently elevated levels of depressive symptoms, as opposed to fluctuating levels, may exhibit a different pattern of UWL. Moreover, the study was not able to account for whether patients received any depression treatment during the study time period. Receipt of pharmacological or psychological treatment for depression could have influenced the degree and course of depression symptomatology. Given the observed bidirectional relationship between depressive symptoms and UWL, successful depression treatment during the study time period could have impacted nutritional

outcomes, as well. The results should be interpreted with caution given the inability to account for the potential influence of depression treatment on outcomes.

Furthermore, the reliance upon a self-report measure of depressed mood necessitated conceptualization of depression at a symptomatic rather than diagnostic level. It is possible that a clinical model of depression could exhibit a different relationship with UWL. Although self-report measures of depressive symptoms are the most common assessment tools used in clinical settings, the patients that would likely be considered for depression treatment would be those exhibiting a certain threshold of clinical severity. Although interpretation of the severity of the depression symptom levels in the present study is less straightforward due the exclusion of two BDI symptoms, levels of depressive symptoms were comparable to those previously reported in HNC patients (Katz et al., 2004), such that scores were in the low- to moderate-severity range. Replication in a sample of patients with more severe depressive symptoms is warranted. Despite the restricted ranges in depressive symptoms observed in this sample, it is notable that significant associations with weight loss were nevertheless detected.

Although the study attempted to account for the influence of important clinical and demographic characteristics, the complexity of HNC tumors, treatment, treatment-related impairment, and interactions between these factors cannot be overstated. Notably, the complex inflammatory processes occurring in cancer patients were not measured in the present study. Further data on these variables could have helped understand the relationship between the outcome variables of interest, as well as pointed to mechanisms between their association.

Future Directions

Future research could supplement this study's findings by incorporating additional measures of nutritional depletion. In particular, information on body composition would enable

analysis of whether weight loss entailed loss of fat or muscle/lean mass. Muscle depletion is associated with poorer functional and survival outcomes, at least in obese cancer patients (Brown et al., 2014; Prado et al., 2008), and provides increased indication of the presence of cancer cachexia. A comprehensive way to achieve this would be to use the cancer-specific Patient-Generated Subjective Global Assessment (Ottery, 1996). In addition to noting changes in weight, presence of eating-related symptoms, and functional capacity, all of which were included in the present study, this validated nutritional assessment also has an oncologist assess metabolic stress level (none, low, moderate, or high) and changes in body composition (measurements of subcutaneous fat and muscle tone). The involvement of physical examination by an oncologist is an obvious challenge for incorporating this measurement into large-scale research. However, one study indicated that combining this assessment with percentage weight loss would enable identification of 18% more true positive cases of moderate/severe malnutrition and 9% more cases of severe malnutrition in HNC patients (Ravasco, Monteiro-Grillo, Vidal, et al., 2003). Although these assessments are unlikely candidates for ultimate implementation into clinical settings, their use in research studies could advance our comprehensive understanding of nutritional changes across the cancer trajectory. Additionally, collection of nutritional lab values, such as serum albumin, would be an informative supplement to weight loss data. Because it is difficult to interpret such values in the absence of information on inflammatory markers, use of an index that combines analysis of inflammatory and nutritional proteins (e.g., the Prognostic Nutritional and Inflammatory Index) would be ideal (Prevost, Joubert, Heutte, & Babin, 2014).

Methodologically strong psychosocial intervention research is lacking in the HNC patient population. Once interventions that successfully improve HRQOL and depression are identified,

additional research should examine whether interventions that reduce either of these symptoms also have crossover effects on reducing UWL. Likewise, research examining the crossover influence of successful nutritional interventions on depressive symptoms is needed. In addition to suggesting flexibility in the target of clinical intervention, the present study indicated that the timing of intervention may also be variable. Although certain time periods during the first year after diagnosis may be more amenable to intervention than others, the differential effects of the timing of interventions have not been closely investigated. Moreover, because slight fluctuations in weight and depressive symptoms are normative in HNC patients, identifying what constitutes meaningful change is an important goal. Intervention research targeting these processes in HNC patients should determine what results in clinically significant changes in weight loss or depressive symptoms, relative to care as usual.

The findings point to the need for future research in this field to employ advanced statistical methods to examine these relationships prospectively across time. The conclusions that emerged from this study are attributable to the utilization of advanced longitudinal modeling. The concurrent covariation model in the present study demonstrated the immediate impact of depressive symptoms on UWL, and vice versa. To the extent that one variable changed on a monthly basis, so did the other variable during that same time interval. These results could be extended by evaluating a cross-lagged growth curve model. Such a model would evaluate a time-delayed (lagged) effect of one variable on the other, such that the temporal precedence of changes in one variable on the other would be examined. For example, it could evaluate whether depressive symptoms assessed at time *t* were associated with changes in PWL at time *t* + 1 (i.e., one to two months later). This could differentiate whether a delayed effect, as opposed to the current study's finding of a concurrent/short-term effect, better characterizes the

relationship between depressive symptoms and UWL. This could be a conceptually relevant analysis, given that the effect of increased weight loss following an increase in depressive symptoms, or the effect of increased depressive symptoms in response to increased weight loss, may take some time to manifest. Such analyses could clarify which variable is more of a driving force for the other, thereby increasing the ability to draw implications regarding causality.

Conclusion

By depicting an ongoing transactional interplay between depressive symptoms and weight loss over the first year after HNC diagnosis, such that changes in either variable across time influenced concurrent deviations in the average trajectory of the other variable, the present study offers significant advancements in our understanding of the trajectories and associations of these important HNC outcomes. It advanced previous research by including patients with diverse disease and treatment characteristics and accounting for these characteristics in analyses, as well as by extending assessments across the entire first year following diagnosis. Given the broad inclusion criteria and robustness of the findings across the sample, the present results generalize to a clinically diverse group of HNC patients. By lengthening the range of the study time period to one year post-diagnosis, the present study comprehensively accounts for the largest extent of changes in depressive symptoms and UWL and is more reflective of longer-term associations between these variables than previous investigations. Additionally, the extent of variables included in the existing dataset offered the ability to thoroughly examine potential control variables. Notably, factors related to disease, treatment, and functional impairment were all included, providing a comprehensive set of control variables and enabling identification of pain and eating-related HRQOL as potential mechanisms of the association.

By using advanced statistical methods that modeled population-level patterns of change while accounting for individual-level differences (i.e., within- and between-subject variability in individual trajectories), this investigation produced novel and nuanced conclusions. This was the first study in HNC patients to use such analyses to examine this topic and to compare the competing temporal precedence models in the same sample. Although other researchers previously suggested the possible existence of a reciprocal association between depressive symptoms and UWL, I was unable to identify any published analyses of such a reciprocal relationship in either the HNC or the broader medical patient population literatures. The present study may be the first of its kind to utilize growth curve modeling covariation analyses to examine the ongoing, reciprocal association between depressive symptoms and UWL.

Overall, the study extends the limited existing research regarding depression and nutritional outcomes in HNC. Through identification of additional ways to predict these relevant clinical outcomes, the results point to important areas for validation and extension of these findings. Ultimately, the emergence of an improved conceptual understanding of the relationship between these variables could contribute to early interventions for physical and mental health outcomes that improve HNC patients' quality and quantity of life.

APPENDIX A: HEAD AND NECK CANCER INVENTORY—EATING SUBSCALE

HEAD AND NECK CANCER INVENTORY

Please read every question very carefully, and circle the answer that best indicates the degree to which the following apply to you.

During the past four weeks:	**No/Not at all**	**A Little**	**Moderately**	**Quite a bit**	**Extremely**	**Other**
9. Have you been bothered by a change in your eating habits?	1	2	3	4	5	
10. Have you been bothered by a change in your teeth or dentures?	1	2	3	4	5	
11. Did you eat slower than others?	1	2	3	4	5	I eat nothing by mouth
12. Have you had problems chewing solid food?	1	2	3	4	5	I eat nothing by mouth
13. Have you had to restrict the foods you can eat?	1	2	3	4	5	I eat nothing by mouth
14. Have changes in or loss of your teeth or dentures made it difficult to chew?	1	2	3	4	5	I eat nothing by mouth
18. Have you been bothered by dryness of the mouth?	1	2	3	4	5	

During the past four weeks:	**Never**	**Rarely**	**Sometimes**	**Frequently**	**Always**	**Not Applicable**
24. Have you used special techniques in order to swallow?	1	2	3	4	5	I eat nothing by mouth
25. How often did you use liquids to wash down soft or solid foods?	1	2	3	4	5	I eat nothing by mouth
27. Has it been necessary to prepare solid foods in a special way in order for you to eat them?	1	2	3	4	5	I eat nothing by mouth

APPENDIX B: BECK DEPRESSION INVENTORY

Following are groups of statements. Please read the entire group of statements in each category, and then pick out the one statement in the group that best describes the way you feel today (at this very moment). Circle the number beside the statement that you have chosen.

1. 0 I do not feel sad
   1 I feel sad
   2 I am sad all the time and I can't stand it
   3 I am so sad or unhappy that I can't stand it

2. 0 I am not particularly discouraged about the future
   1 I feel discouraged about the future
   2 I feel that I have nothing to look forward to
   3 I feel that the future is hopeless and that things cannot improve

3. 0 I do not feel like a failure
   1 I feel that I have failed more than the average person
   2 As I look back on my life all I can see is a lot of failure
   3 I feel that I am a complete failure as a person

4. 0 I get as much satisfaction out of things as I used to
   1 I don't enjoy things the way I used to
   2 I don't get real satisfaction out of anything anymore
   3 I am dissatisfied or bored with everything

5. 0 I don't feel particularly guilty
   1 I feel guilty a good part of the time
   2 I feel quite guilty most of the time
   3 I feel guilty all the time

6. 0 I don't feel that I am being punished
   1 I feel I may be punished
   2 I expect to be punished
   3 I feel that I am being punished

7. 0 I don't feel disappointed in myself
   1 I am disappointed in myself
   2 I am disgusted with myself
   3 I hate myself

8. 0 I don't feel that I am worse than anybody else
   1 I am critical of myself for my weaknesses and mistakes
   2 I blame myself all the time for my faults
   3 I blame myself for everything bad that happens

9. 0 I don't have any thoughts of killing myself

1 I have thoughts of killing myself, but I would not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

10. 0 I don't cry any more than usual
1 I cry more now than I used to
2 I cry all the time now
3 I sued to be able to cry, but now I can't cry even though I want to

11. 0 I am no more irritated now than I ever am
1 I get annoyed or irritated more easily than I used to
2 I feel irritated all the time now
3 I don't get irritated at all by the things that used to irritate me

12. 0 I have not lost interest in other people
1 I am less interested in other people than I used to be
2 I have lost most of my interest in other people
3 I have lost all of my interest in other people

13. 0 I make decisions about as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty making decisions than before
3 I can't make decisions at all anymore

14. 0 I don't feel that I look any worse than I used to
1 I am worried that I am looking old or unattractive
2 I feel that there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly

15. 0 I can work about as well as before
1 It takes extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can't do any work at all

16. 0 I can sleep as well as usual
1 I don't sleep as well as I used to
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

17. 0 I don't get any more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything

18. 0 My appetite is not worse than usual

1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite anymore

19. 0 I haven't lost much weight, if any, lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds

I am purposely trying to lose weight by eating less: ……Yes___..No____

20. 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains or upset stomach or constipation
2 I am very worried about physical problems and it is hard to think of much else
3 I am so worried about my physical problems, I cannot think about anything else

21. 0 I have not noticed any recent change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

Note. Items 18 and 19 were excluded in primary analyses.

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