Sleep quality in head and neck cancer patients

Angelina Maria Mirna Santoso

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Weary with toil, I haste me to my bed,

The dear repose for limbs with travel tired;

But then begins a journey in my head

To work my mind, when body's work's expired …

-William Shakespeare (Sonnet 27)

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Chapter I

General Introduction

A good night sleep is essential for optimal health and wellbeing of each individual. Among cancer patients in general, sleep quality and sleep quantity are often compromised[1]. In this thesis, I will refer to these problems as 'sleep disturbances'. It is important to detect those sleep disturbances as early as possible already before start of treatment, since they are associated with shorter survival[2] and worse health related quality of life (HRQoL)[3, 4]. Moreover, sleep disturbances, which are often initiated at cancer diagnosis and exacerbated by cancer treatment, may persist until long after treatment completion[5, 6].

There is still a lot we don't know about sleep disturbances among head and neck cancer (HNC) patients. We do know that HNC patients often suffer from psychological and physical impacts due to cancer itself or its treatment[7] and that this may make them vulnerable to have sleep disturbances. Therefore, this thesis aims to provide more insight into sleep quality and sleep disturbances in HNC patients.

In this introduction chapter, I will first describe the epidemiology, risk factors, and clinical courses of HNC as well as the quality of life of these patients. Then, I will discuss physiological aspects of sleep. Subsequently, I will describe the classifications of sleep disturbances and various methods to measure them, followed by an overview of the existing literature on sleep disturbances in the general population and in cancer patients. Finally, I will describe the research aims and outline of this thesis.

Head and neck cancer: epidemiology, risk factors, and clinical courses

Every year, about 600,000 people in the world are newly diagnosed with head and neck cancer (HNC)[8]. In the Netherlands, the incidence of HNC in the past decade has remained stable at approximately 3,000 patients per year[9]. The incidence rate is twice as high in men than in women and about half of the patients are aged 60 – 74 years[9]. The most common subtypes of HNC in the Netherlands are squamous cell carcinomas located in the oral cavity, oropharynx, hypopharynx, or larynx (Figure 1)[10, 11]. The most important risk factors of HNC are smoking and excessive alcohol consumption[8,12]. Additionally, human papilloma virus (HPV) infection is a major risk factor for HNC in the oropharynx[13].

The 5-year survival of HNC between 2000 and 2007 in Europe was 25% - 59%[14]. Worldwide, there is a stable (for laryngeal cancer) to increasing trend (for other HNC subsites) of the survival rates[14]. This is also found in the Netherlands: in the past decades there is a stable 5-year survival rate of 70% among laryngeal cancer patients and an increasing survival rate among oropharyngeal (36% in 1989 – 1994 to 48% in 2007 – 2011), oral (56% to 62%), and hypopharyngeal cancer patients (27% to

33%)[15]. The increasing survival rate can be attributed to better screening, diagnosis, and treatment modalities for HNC[14, 15], as well as due to increase of HPV-related HNC which generally has better treatment outcomes[16].

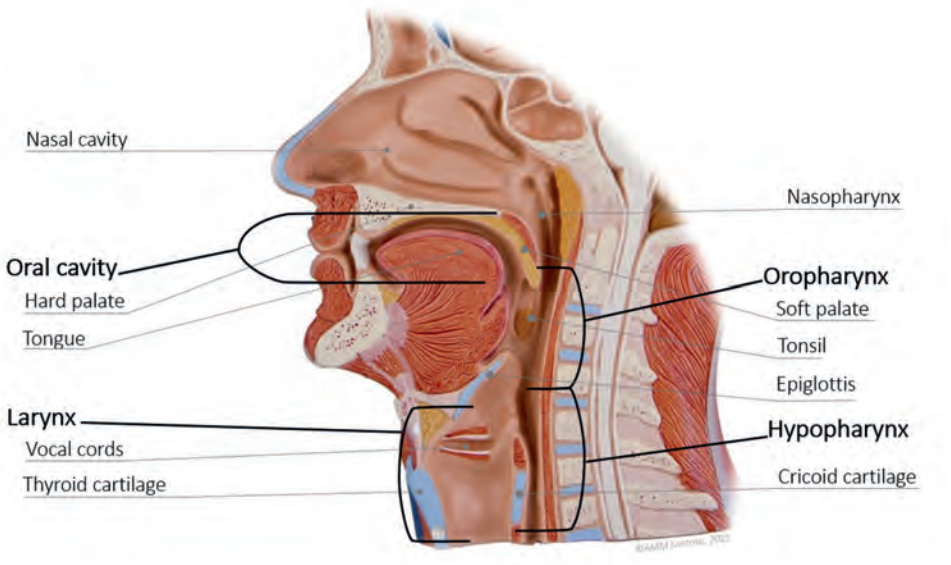

Figure 1 Anatomical locations of head and neck cancer. *Modified image from Opsorman/Shutterstock.com.*

The journey of patients with primary HNC from diagnosis to treatment completion is usually as follows (**Figure 2**). Patients initially visit the healthcare professional with symptoms characterizing HNC, such as oral or throat pain, changes in the tongue, persistent oral ulcers, teeth problems, swallowing problems, neck lump, hoarseness, or weight loss[17, 18]. To confirm HNC diagnosis and staging, a thorough anamnesis is needed to collect information on other relevant symptoms and medical history. Alongside there is usually a series of examinations: physical examination, endoscopy, biopsy, lymph node aspiration, dental evaluation, and imaging techniques (e.g., computed tomography (CT) scan, chest X-ray, and magnetic resonance imaging (MRI))[17]. Based on the findings, the staging of HNC can be determined using the TNM criteria: tumor (the extent of the primary tumor), node (the extent of tumor spread to the regional lymph nodes), and metastasis (the presence of distant metastasis)[19]. This TNM staging can be further classified into prognostic stages, which range from 0 (carcinoma in situ; good prognosis) to IV (poor prognosis)[19].

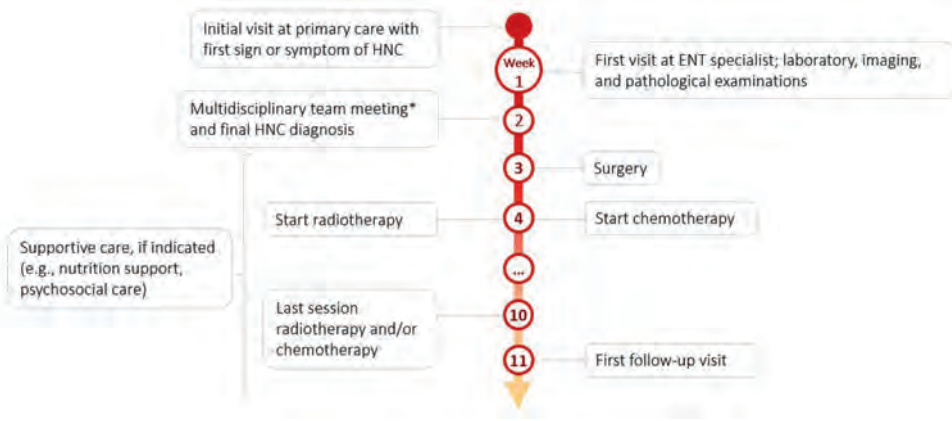

Figure 2 Illustration of head and neck cancer journey from diagnosis to treatment completion.
* Multidisciplinary team meeting varies slightly between hospitals, but it usually involves otolaryngology specialists, oral surgeons, oncology specialists from internal medicine, radiotherapy specialists, and case managers or oncology nurses. Supportive care providers (e.g., oral hygienist, speech therapist, psychologist, dietician, physiotherapist, medical-social workers) can be either included in the meeting early on or contacted by the case manager after the initial meeting.

Clinical factors such as HNC sub-site, TNM staging, patients' fitness and comorbidity status[20, 21], as well as patients' preferences[22] determine the treatment modality for HNC. Single modality treatment is usually prescribed to patients with early-stage of HNC (i.e., carcinoma in situ, stage I, and stage II) and consists of surgery only (i.e., resection of primary tumor with/without its adjacent structure and with/without lymph nodes resection) or radiotherapy (RT) only[20, 21]. Combined modality treatment is prescribed for advanced-stage patients (i.e., stage III and IV) and consists of either chemo-radiotherapy (CRT) only or surgery followed by RT or CRT[20, 21]. The side effects of these treatment modalities can be categorized into: (i) local side effects, such as mucositis (oral pain), xerostomia (dry mouth), dysphagia (swallowing problems), speech problems, osteoradionecrosis (bone damage due to RT/CRT), and fibrosis (tissue scarring); and (ii) systemic side effects (as a direct effect of treatment, such as kidney toxicity, or as a secondary effect, such as malnutrition)[21, 23]. These side effects inevitably affect the patients' quality of life (QoL) during their cancer journey.

Quality of life of HNC patients

The physical symptoms of HNC, the psychological impact of HNC diagnosis, as well as the side effects of HNC treatment often compromise the QoL of HNC patients. Moreover, various domains of QoL may reach worst levels at different treatment phases[24]. Global QoL often deteriorates from diagnosis (before treatment starts) until 6 months after treatment, then gradually improves and often reaches its normal level at 1-year after treatment[25-27]. Emotional distress, especially anxiety, usually reaches its worst level before start of treatment and gradually improves afterwards[28-31]. Other symptoms (i.e., teeth problems, dry mouth, dyspnea, drowsiness, fatigue, oral pain, appetite loss, sexuality problems, and nausea) often reach the worst levels during treatment up to six months afterwards[27, 28, 30, 32]. At 1 year after treatment completion, most of the symptoms seem to recover to their pre-treatment levels[24, 25], with exception of physical functioning, xerostomia, sticky saliva, and fatigue[25, 27]. In addition, swallowing and chewing problems remain to be a significant problem among patients with oropharyngeal cancer at 1 year after treatment or later on[33]. These symptoms, individually or simultaneously, may play a role in sleep disturbances in HNC patients.

Before moving further to the paragraph on sleep disturbances among HNC patients, which is the main subject of this thesis, I will first review the existing knowledge on the physiology of sleep and the various sleep disturbances measures.

The physiology of sleep

A good night's sleep consists of several sleep cycles. Each sleep cycle lasts about one and a half to two hours and consists of several stages as measured on the brain wave, eye movements, and muscle activities through polysomnography[34, 35]. The first four stages of sleep are referred to as non-rapid eye movement (NREM) sleep. Stage 1 takes place as one falls asleep: the brainwave turns slower and its frequency turns low, the eyes move slowly and predominantly horizontally, and the muscles relax. After a few minutes of undisturbed first phase, stage 2 takes place: the slow brain wave is interrupted by rapid waves (called 'sleep spindles'), the eye movement stops, and muscle relaxation is mixed with periods of contractions. The brain wave further slows down in stage 3 and stage 4, which collectively referred to as 'slow-wave' or deep sleep. The NREM sleep is followed by REM sleep, which is characterized by brain wave activity similar to that of stage 1, bursts of rapid eye movement, and complete muscle relaxation. The duration of REM increases gradually through the night as the full sleep cycle of NREM-REM repeats. It is hypothesized that the whole NREM-REM sleep cycle plays important role in energy conservation[36] and memory consolidation; NREM

sleep specifically in consolidation of newly acquired explicit memory (e.g. recollecting events, remembering names)[37] and REM sleep in consolidation of implicit memory (e.g. learning a skill) and emotional regulation[37-39].

Our daily sleep-wake pattern follows the circadian rhythm (in Latin, *circa* means "approximately" and *diem*, which means "day"), which takes slightly longer than 24 hours. The circadian rhythm is regulated by an internal biological clock in the hypothalamus which is largely influenced by daylight as an external signal (*zeitgeber*) [40]. This regulation involves a complex neuro-endocrine mechanism, including the regulation of brain neurotransmitters[41].

An intact circadian rhythm is essential for good sleep and a good sleep is essential to regulate the body's response upon stress, especially by preserving the activity of hypothalamic-pituitary-adrenal (HPA) axis and the inflammatory system[42, 43]. The level of cortisol, a hormone produced by adrenal gland as part of the HPA-axis, increases dramatically at awakening and gradually decreases throughout the day until it reaches the lowest level during sleep[44]. It is hypothesized that physical or psychological stress induces activation of the HPA-axis, increasing the production of cortisol which further initiates multiple responses such as increase of glucose level in the blood, increase of heart rate, and inhibition of the inflammatory system[45]. Poor sleep quality in particular disturbs the normal circadian rhythm of HPA-axis[46] and enhances HPA-axis activation during stressful situation[47]. Eventually, persistent poor sleep quality reduces HPA-axis reactivity upon stress, but retains the high production of cortisol[42, 47]. This prolonged HPA-axis activation is hypothesized to induce cortisol resistance in immune cells, impairing the anti-inflammatory effect of cortisol[43]. This vicious circle may explain the link between persistent poor sleep and chronic inflammatory diseases, such as cardiovascular disease, diabetes mellitus, autoimmune diseases, and neurodegenerative disorders[42, 43, 48].

Sleep disturbances: diagnosis criteria, measurements, and terminologies

The clinical diagnosis criteria of sleep disturbances as sleep disorders (also referred to as 'sleep-wake disorders') are described in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V)[49] and the International Classification of Sleep Disorders (ICSD-3)[50]. Both the DSM and the ICSD-3 distinguish six major sleep disorders[49, 51] and will be listed here based on their prevalence. First, insomnia disorder, which has been acclaimed as the most common sleep disorder among people in the general population[52] as well as among cancer patients[53]. Insomnia is characterized by difficulty in initiating or maintaining sleep, early morning or night-

time awakening, and daytime impairments due to sleep difficulties[54]. Second, sleep-related breathing disorders, which are characterized by respiratory events (i.e., snoring and breathing pauses) during sleep[51]. The most common form of sleep-related breathing disorders is obstructive sleep apnea (OSA) and its prevalence is 9% to 38% in general population[55]. Third, central disorders of hypersomnolence, which is characterized by excessive daytime sleepiness without the presence of other sleep disorder[51]. Its prevalence is between 5% and 15% in general population[56].

The remaining sleep disorders are less common; these include circadian rhythm sleep-wake disorders (where the biological clock is out of sync with sleep-wake schedule required by the social or professional environment, e.g. a delayed phase sleep syndrome, shift work disorder), parasomnias (unusual behaviors in the night e.g., sleepwalking, night terrors), and sleep-related movement disorders (e.g., restless legs syndrome)[49, 51] . The prevalence of these sleep disorders among cancer patients is difficult to ascertain, since available studies used small sample sizes and various definitions of sleep disorders[57, 58].

There are two ways to assess sleep disturbance: objectively and subjectively. The golden standard of objective sleep measurement is polysomnography which simultaneously measures brain activity, eye movement, respiratory activity, heart rate, blood oxygen concentration, body position, and muscle activity during sleep[59]. Polysomnography usually requires the patient to stay overnight in a sleep laboratory, making this method costly and burdensome. Although polysomnography can also be performed at home, the patient still needs to visit a laboratory to apply all the measurement probes and to take them off the following day. Sleep can also be assessed subjectively by using sleep diaries and questionnaires. Sleep diaries require the patients to write down their bedtime, the time that they are awake in bed and asleep, the time they get out of bed, and additional complaints related to their sleep. Questionnaires are also used to measure these aspects of sleep along with self-perceived sleep quality, possible disturbances, as well as consequences of poor sleep on QoL. The advantage of a questionnaire over a sleep diary is that a questionnaire is less burdensome to patients[60]. For cancer patients, there are two widely-used questionnaires with sufficient reliability and validity, the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI)[57, 61]. The PSQI has an advantage over ISI as a screening measure in routine oncological care as it covers multiple domains to identify not only symptoms of insomnia but also of other sleep disorders[62, 63], which may be useful to guide further investigation accordingly.

In the literature and in clinical care, various sleep-related terminologies are used, which often leads to confusion. In this thesis, any sleep symptoms or disorders which compromise sleep quality are referred to as ‘sleep disturbances’. This term has been

used in the current literature as a collective term to describe both disruption of sleep as symptoms (measured by subjective sleep measures) and sleep disorders (based on a set of diagnosis criteria either defined by DSM or ICSD). Those who have sleep disturbance as symptoms may not meet all diagnosis criteria for a sleep disorder[64]. However, sleep disturbance as symptoms may develop into a full-blown sleep disorder and its presence may indicate an existing sleep disorder. A sleep disorder is diagnosed when a set of diagnosis criteria is met. On the other side, sleep disturbance symptoms/complaints are considered meaningful when their level surpasses the cut-off point of the questionnaire. In this thesis, we referred to the latter as "poor sleep quality", defined by a PSQI total score of > 5.

Sleep disturbances in the general population and in cancer patients

Many factors are known to alter sleep quality both among general population and cancer patients. First of all, age and sex are the most consistent risk factors of sleep disturbances. As people get older, their sleep pattern changes[65, 66]. Older people spend less time in the deep sleep phases and more in light sleep. As a result they also wake up more frequently during the night. Elderly persons also need less hours of sleep. Females of all age groups are more likely to have insomnia symptoms than men[67]. Also, lifestyle factors (e.g., lack of physical activity, alcohol consumption), physical conditions (e.g., pain, obesity), psychological distress (e.g., anxiety, depression), and medications (e.g., anti-depressants, opioid painkillers) are known to increase the risk of sleep disturbances[66]. These risk factors are also relevant in sleep disturbances among cancer patients[68, 69] . In addition, some factors are specific for cancer patients and may increase their risk of having poor sleep. Cancer itself (depends on its location) may cause pain or breathing difficulty that disturbs sleep. Receiving the diagnosis of cancer often makes patients anxious or worried; they are often concerned about the prognosis and possible consequences of cancer and its treatment on their own life and that of their families[70, 71]. As the treatment starts, sleep quality may be further disturbed by side effects of treatment as well as suboptimal sleep environment during hospital admissions[72, 73]. Furthermore, cancer patients who have sleep disturbances often develop certain behaviors such as taking naps during the day or taking sleep medication, in the hope to relieve their sleep disturbances. In fact we know that these behaviors maintain sleep problems since they disturb the biological clock and they also diminish the need to sleep. Therefore, these behaviors ultimately might lead to persistent sleep disturbances[72].

Among HNC patients specifically, information on the prevalence, risk factors, and the persistence of poor sleep quality is scarce. There is an urgency to investigate this more closely, as a longitudinal study examining health-related QoL among HNC

patients found that sleep disturbance (measured by a single question) before treatment is a significant predictor of 2-year disease-free survival[74].

Research aims and outline of this thesis

This thesis includes four research aims, outlined in the following four chapters. The first aim was to examine the available literature on sleep disturbances among HNC patients to establish the prevalence of sleep disturbances of HNC patients during all treatment phases. For this aim, we performed a systematic review and meta-analysis of prevalence (Chapter 2). The second aim was to examine the risk factors of poor sleep quality before HNC treatment starts. For this aim, a cross-sectional study was performed using data from a large multicentre cohort study among HNC patients in several HNC centres in the Netherlands (Chapter 3). The third aim was to investigate the trajectories of poor sleep quality among HNC patients from diagnosis up to 6 months after treatment completion (Chapter 4). The fourth aim was to examine the relationship between poor sleep quality, its commonly co-occurring symptoms (i.e. psychological distress, fatigue, and pain), and biological parameters (i.e. cortisol level and inflammatory markers) among HNC patients prior to treatment (Chapter 5). Finally, the findings of these studies are discussed in Chapter 6, together with the available literature, implications for clinical care, and recommendations for future research.

References

1. Palesh OG, Roscoe JA, Mustian KM, Roth T, Savard J, Ancoli-Israel S, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center–Community Clinical Oncology Program. Journal of clinical oncology. 2010;28(2):292.
2. Gottfried T, Kamer I, Salant I, Urban D, Lawrence YR, Onn A, et al. Self-reported sleep quality as prognostic for survival in lung cancer patients. Cancer Management and Research. 2020;12:313.
3. Dean GE, Sabbah EA, Yingrengreung S, Ziegler P, Chen H, Steinbrenner LM, et al. Sleeping with the enemy: sleep and quality of life in patients with lung cancer. Cancer nursing. 2015;38(1):60-70.
4. Mystakidou K, Parpa E, Tsilika E, Pathiaki M, Gennatas K, Smyrniotis V, et al. The relationship of subjective sleep quality, pain, and quality of life in advanced cancer patients. Sleep. 2007;30(6):737-42.
5. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. Journal of clinical oncology. 2011;29(26):3580-6.
6. Fleming L, Gillespie S, Espie CA. The development and impact of insomnia on cancer survivors: a qualitative analysis. Psycho-oncology. 2010;19(9):991-6.
7. Shepherd KL, Fisher SE. Prospective evaluation of quality of life in patients with oral and oropharyngeal cancer: from diagnosis to three months post-treatment. Oral oncology. 2004;40(7):751-7.
8. Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. Oncology. 2016;91(1):13-23.
9. IKNL. Incidentie, Hoofd-halskanker, Aantal: NKR-cijfers / Integraal Kankercentrum Nederland; 2022 [26 January 2023]. Available from: https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=526&fs%7Ctumor_id=78&fs%7Cregio_id=550&fs%7Cperiode_id=586%2C587%2C588%2C589%2C590%2C591%2C592%2C593%2C594%2C563%2C562&fs%7Cgeslacht_id=645&fs%7Cleeftijdsgroep_id=678&fs%7Cjaren_na_diagnose_id=688&fs%7Ceenheid_id=704&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=epidemiologie_id&ts%7CrowDimensions=periode_id&ts%7CcolumnDimensions=&lang%7Clanguage=nl.
10. de Ridder M, Balm A, de Jong RB, Terhaard C, Takes R, Slingerland M, et al. Variation in head and neck cancer care in the Netherlands: A retrospective cohort evaluation of incidence, treatment and outcome. European Journal of Surgical Oncology (EJSO). 2017;43(8):1494-502.
11. Halmos G, Bras L, Siesling S, van der Laan B, Langendijk J, van Dijk B. Age-specific incidence and treatment patterns of head and neck cancer in the Netherlands—A cohort study. Clinical otolaryngology. 2018;43(1):317-24.
12. Hashibe M, Brennan P, Chuang S-c, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiology Biomarkers & Prevention. 2009;18(2):541-50.
13. Tumban E. A current update on human papillomavirus-associated head and neck cancers. Viruses. 2019;11(10):922.
14. Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, Licitra L, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. European journal of cancer. 2015;51(15):2130-43.
15. Braakhuis BJ, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in the Netherlands between 1989 and 2011. Oral oncology. 2014;50(7):670-5.
16. Mehanna H, Olaleye O, Licitra L. Oropharyngeal cancer–is it time to change management according to human papilloma virus status? Current opinion in otolaryngology & head and neck surgery. 2012;20(2):120-4.

17. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. New England Journal of Medicine. 2001;345(26):1890-900.
18. Alho O-P, Teppo H, Mäntyselkä P, Kantola S. Head and neck cancer in primary care: presenting symptoms and the effect of delayed diagnosis of cancer cases. Cmaj. 2006;174(6):779-84.
19. Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and neck cancers—major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA: a cancer journal for clinicians. 2017;67(2):122-37.
20. Ho AS, Yao M. Treatment planning considerations. Head & Neck Cancer: Current Perspectives, Advances, and Challenges. 2013:471-93.
21. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and neck cancers, version 2.2020, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network. 2020;18(7):873-98.
22. Dronkers EA, Mes SW, Wieringa MH, van der Schroeff MP, Baatenburg de Jong RJ. Noncompliance to guidelines in head and neck cancer treatment; associated factors for both patient and physician. BMC cancer. 2015;15(1):1-10.
23. Jategaonkar AA, Badhey AK, Chai RL. Treatment-Related Patient Outcomes for Head and Neck Cancer. Head and Neck Cancer: Psychological and Psychosocial Effects. 2020:21-38.
24. Babin E, Sigston E, Hitier M, Dehesdin D, Marie J, Choussy O. Quality of life in head and neck cancers patients: predictive factors, functional and psychosocial outcome. European archives of oto-rhino-laryngology. 2008;265:265-70.
25. So W, Chan R, Chan D, Hughes B, Chair S, Choi K, et al. Quality-of-life among head and neck cancer survivors at one year after treatment–a systematic review. European journal of cancer. 2012;48(15):2391-408.
26. Wissinger E, Griebsch I, Lungershausen J, Byrnes M, Travers K, Pashos CL. The humanistic burden of head and neck cancer: a systematic literature review. PharmacoEconomics. 2014;32:1213-29.
27. Dahele M, Tol JP, Vergeer MR, Jansen F, Lissenberg-Witte BI, Leemans CR, et al. Is the introduction of more advanced radiotherapy techniques for locally-advanced head and neck cancer associated with improved quality of life and reduced symptom burden? Radiotherapy and Oncology. 2020;151:298-303.
28. Bjordal K, Ahlner-Elmqvist M, Hammerlid E, Boysen M, Evensen JF, Biörklund A, et al. A prospective study of quality of life in head and neck cancer patients. Part II: Longitudinal data. The Laryngoscope. 2001;111(8):1440-52.
29. Aoki T, Ota Y, Suzuki T, Denda Y, Aoyama K-I, Akiba T, et al. Longitudinal changes in the quality of life of oral cancer patients during the perioperative period. International Journal of Clinical Oncology. 2018;23:1038-45.
30. Allen-Ayodabo CO, Eskander A, Davis LE, Zhao H, Mahar AL, Karam I, et al. Symptom burden among head and neck cancer patients in the first year after diagnosis: Association with primary treatment modality. Oral oncology. 2019;99:104434.
31. Van Beek F, Jansen F, Mak L, Lissenberg-Witte B, Buter J, Vergeer M, et al. The course of symptoms of anxiety and depression from time of diagnosis up to 2 years follow-up in head and neck cancer patients treated with primary (chemo) radiation. Oral Oncology. 2020;102:104576.
32. Melissant HC, Jansen F, Schutte LE, Lissenberg-Witte BI, Buter J, Leemans CR, et al. The course of sexual interest and enjoyment in head and neck cancer patients treated with primary (chemo) radiotherapy. Oral Oncology. 2018;83:120-6.
33. Michaelsen SH, Grønhøj C, Michaelsen JH, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: a systematic review and meta-analysis of 1366 patients. European Journal of Cancer. 2017;78:91-102.
34. Altevogt BM, Colten HR. Sleep disorders and sleep deprivation: an unmet public health problem. 2006.

35. Monti J, Monti D. Human sleep: sleep and quality of life in clinical medicine. New York: Humana Press; 2008.
36. Latifi B, Adamantidis A, Bassetti C, Schmidt MH. Sleep-wake cycling and energy conservation: role of hypocretin and the lateral hypothalamus in dynamic state-dependent resource optimization. Frontiers in neurology. 2018;9:790.
37. Ackermann S, Rasch B. Differential effects of non-REM and REM sleep on memory consolidation? Current neurology and neuroscience reports. 2014;14:1-10.
38. Tempesta D, Socci V, De Gennaro L, Ferrara M. Sleep and emotional processing. Sleep medicine reviews. 2018;40:183-95.
39. Zeng S, Lin X, Wang J, Hu X. Sleep's short-term memory preservation and long-term affect depotentiation effect in emotional memory consolidation: behavioral and EEG evidence. Sleep. 2021;44(11):zsab155.
40. Roenneberg T, Klerman EB. Chronobiology. A short introduction. Somnologie. 2019(3):142-6.
41. Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of sleep and wakefulness. Physiological reviews. 2012.
42. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep medicine reviews. 2008;12(3):197-210.
43. Irwin MR. Sleep and inflammation: partners in sickness and in health. Nature Reviews Immunology. 2019;19(11):702-15.
44. Clow A, Hucklebridge F, Stalder T, Evans P, Thorn L. The cortisol awakening response: more than a measure of HPA axis function. Neuroscience & Biobehavioral Reviews. 2010;35(1):97-103.
45. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychological bulletin. 2004;130(3):355.
46. Pulopulos MM, Hidalgo V, Puig-Perez S, Montoliu T, Salvador A. Relationship between cortisol changes during the night and subjective and objective sleep quality in healthy older people. International Journal of Environmental Research and Public Health. 2020;17(4):1264.
47. van Dalfsen JH, Markus CR. The influence of sleep on human hypothalamic–pituitary–adrenal (HPA) axis reactivity: A systematic review. Sleep medicine reviews. 2018;39:187-94.
48. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nature medicine. 2019;25(12):1822-32.
49. Association AP. Sleep-Wake Disorders. Diagnostic and Statistical Manual of Mental Disorders, (DSM-5). Arlington, VA: American Psychiatric Association. 2013.
50. American Academy of Sleep M. International classification of sleep disorders. Third edition. ed. Darien, IL: American Academy of Sleep Medicine; 2014.
51. Zucconi M, Ferri R. Assessment of sleep disorders and diagnostic procedures. Eur Sleep Res Soc. 2014;23(95):110.
52. Ferrie JE, Kumari M, Salo P, Singh-Manoux A, Kivimäki M. Sleep epidemiology—a rapidly growing field. Oxford University Press; 2011. p. 1431-7.
53. Berger AM, Miller JN, Shade MY. Sleep disorders. Supportive Cancer Care. 2016:207-21.
54. Morin CM, Espie CA. Clinical features of insomnia. Insomnia: A Clinical Guide to Assessment and Treatment. 2004:13-25.
55. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep medicine reviews. 2017;34:70-81.
56. Partinen M. Epidemiology of sleep disorders. Handbook of clinical neurology. 2011;98:275-314.
57. Otte JL, Carpenter JS, Manchanda S, Rand KL, Skaar TC, Weaver M, et al. Systematic review of sleep disorders in cancer patients: can the prevalence of sleep disorders be ascertained? Cancer medicine. 2015;4(2):183-200.

58. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. Sleep medicine reviews. 2004;8(3):199-212.
59. BaHammam AS, Gacuan DE, George S, Acosta KL, Pandi-Perumal SR, Gupta R. Polysomnography I: procedure and technology. Synopsis of Sleep Medicine. 2016:443-56.
60. Mallinson DC, Kamenetsky ME, Hagen EW, Peppard PE. Subjective sleep measurement: comparing sleep diary to questionnaire. Nature and Science of Sleep. 2019:197-206.
61. Redeker NS, Pigeon WR, Boudreau EA. Incorporating measures of sleep quality into cancer studies. Supportive Care in Cancer. 2015;23:1145-55.
62. Klingman KJ, Jungquist CR, Perlis ML. Questionnaires that screen for multiple sleep disorders. Sleep Medicine Reviews. 2017;32:37-44.
63. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep. 2006;29(9):1155-73.
64. McGinty HL, Carroll AJ, Sanford SD. Sleep disturbance in cancer survivors. Clinical handbook of insomnia. 2017:221-42.
65. Dijk D-J, Duffy JF, Czeisler CA. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. Chronobiology international. 2000;17(3):285-311.
66. Morin CM, Espie CA. The Basics of Sleep. Insomnia: A Clinical Guide to Assessment and Treatment. 2004:1-11.
67. Zhang B, Wing Y-K. Sex differences in insomnia: a meta-analysis. Sleep. 2006;29(1):85-93.
68. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. Journal of clinical oncology. 2001;19(3):895-908.
69. Induru RR, Walsh D. Cancer-related insomnia. American Journal of Hospice and Palliative Medicine®. 2014;31(7):777-85.
70. List MA, Lee Rutherford J, Stracks J, Haraf D, Kies MS, Vokes EE. An exploration of the pretreatment coping strategies of patients with carcinoma of the head and neck. Cancer. 2002;95(1):98-104.
71. Moore K, Ford P, Farah C. "I have quality of life… but…": exploring support needs important to quality of life in head and neck cancer. European Journal of Oncology Nursing. 2014;18(2):192-200.
72. Garland SN, Barg FK, Cakouros B, Gehrman P, DuHamel KN, Mao JJ. A qualitative examination of the factors related to the development and maintenance of insomnia in cancer survivors. Palliative & supportive care. 2019;17(2):221-6.
73. Wesselius HM, Van Den Ende ES, Alsma J, Ter Maaten JC, Schuit SC, Stassen PM, et al. Quality and quantity of sleep and factors associated with sleep disturbance in hospitalized patients. JAMA internal medicine. 2018;178(9):1201-8.
74. Yang CJ, Roh J-L, Kim M-J, Lee S-w, Kim S-B, Choi S-H, et al. Pretreatment quality of life as a prognostic factor for early survival and functional outcomes in patients with head and neck cancer. Quality of Life Research. 2016;25:165-74.

Chapter II

Prevalence of sleep disturbances among head and neck cancer patients: a systematic review and meta-analysis

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Summary

This systematic review and meta-analysis aim to investigate the prevalence rates of various types of sleep disturbances among head and neck cancer (HNC) patients before, during, and after cancer treatment. We performed a systematic search on PubMed, Embase, CINAHL, and PsycINFO to find studies that reported the prevalence of any type of sleep disturbance among adult HNC patients. Meta-analyses of prevalence were performed using random effects models, with I^2 values to indicate the extent of heterogeneity. In total, 29 studies of accumulatively 2,315 HNC patients were included. The quality of the studies was fairly low and the heterogeneity was high. Studies on three types of sleep disturbances were found: insomnia (17 studies), hypersomnolence (12 studies), and sleep-related breathing disturbances (14 studies). The prevalence of insomnia was 29% (95% CI 20-41%) before treatment, 45% (95%CI 33-58%) during treatment, and 40% (95%CI 24-58%) after treatment, while for hypersomnolence the prevalence was 16% (95% CI 7-32%) before treatment and 32% (95% CI 20-48%) after treatment. The prevalence of sleep-related breathing disturbances before and after treatment was 66% (95% CI 44-82%) and 51% (95% CI 34-67%), respectively. These results imply that sleep disturbances are highly prevalent among HNC patients before, during, and after treatment.

Introduction

Every year more than half a million people in the world are diagnosed with head and neck cancer (HNC) [1]. Among this population, sleep disturbances have been hypothesized to be highly prevalent [2]. Two major risk factors of HNC, smoking and alcohol abuse [3], are associated with sleep disturbances in the general population [4, 5]. Patients with HNC also often experience specific symptoms which may be associated with their disease and treatment phase, for example xerostomia (dry mouth) and pain in the mouth/throat area [6]. These symptoms are known to be strong predictors of sleep disturbances among HNC patients [7]. Moreover, being diagnosed with and treated for HNC is stressful. Previous studies have demonstrated that psychological distress including symptoms of anxiety and depression among HNC patients is highly prevalent [8, 9] and is associated with sleep disturbances [10].

According to the third edition of the international classification of sleep disorders (ICSD-3), there are seven major diagnosis of sleep disorders: 1) insomnia, 2) sleep-related breathing disorders, 3) central disorders of hypersomnolence, 4) circadian rhythm sleep-wake disorders, 5) parasomnias, 6) sleep-related movement disorders, and 7) other sleep disorders [11]. The diagnosis of these sleep disorders is based on subjective measures, such as sleep diaries, interview, sleep consultation, and questionnaires, as well as objective measures, such as polysomnography (PSG) and actigraphy [12]. Among these distinct types of sleep disturbances, insomnia, hypersomnolence, and sleep-related breathing disturbances are expected to be commonly experienced by HNC patients.

Firstly, insomnia entails difficulties falling or staying asleep or sleep of poor quality, leading to daytime disabilities [13]. Insomnia is the most common type of sleep disturbances among the general population [12]; this problem is even more prevalent in cancer patients [14]. Secondly, hypersomnolence is characterized by excessive daytime sleepiness and only diagnosed in the absence of other sleep disorders which might cause insufficient sleep and hence more sleepiness during the day. However, in cancer patients hypersomnolence is often reported as a symptom while the exact cause is unknown [15]. Factors found to be related to hypersomnolence are, for example, radiotherapy, chemotherapy, and opiates (i.e., a commonly prescribed pain-relieving medication among HNC patients) [16-19]. Finally, obstructive sleep apnea (OSA), one of the most prominent form of sleep-related breathing disturbances, involves frequent breathing pauses due to narrow or obstructed upper airways [20]. HNC patients are at risk for this condition because the pharyngeal and craniofacial structures are often altered due to cancer itself or its treatment side effects.

Despite its importance, precise estimates of the prevalence of sleep disturbances among HNC patients are lacking [21]. Previous reviews reported prevalence rates ranging from

8% to 100% among cancer patients [22-25]. To the extent of our knowledge, no meta-analysis has been performed on the prevalence of all different types of sleep disturbances among HNC patients. Therefore, the aim of this study is to systematically review the prevalence of all types of sleep disturbances among HNC patients before, during, and after treatment using meta-analysis approach.

Methods

Literature search

The search strategy was part of another systematic review which examined sleep disturbances among mixed cancer patients (Prospero ID CRD42018088119) [26]. A comprehensive search was performed in the following bibliographic databases: Pubmed, Embase, CINAHL, and PsycINFO. Databases were searched from inception up to November 2017. Synonyms and closely related words were searched as index terms or free-text words for the following terms: cancer (e.g., cancer, malignancy, and carcinoma), sleep disturbances (e.g., sleep problems, disturbed sleep, parasomnia, hypersomnolence, and circadian rhythm disturbance), and epidemiological studies (e.g., epidemiological studies, cross-sectional, and observational). All terms related to distinct forms of sleep disturbance, based on the ICSD-3, as well as different index terms for each bibliographic database were listed. The complete description of our search strategy is available in Appendix 1.

An information specialist from the medical library (de Vries R) provided advice on the literature search. Additional relevant full-texts were hand-searched from the reference list of the included studies and relevant reviews.

Inclusion and exclusion criteria

Studies which met the following inclusion criteria were included in this systematic review: 1) measuring any type of sleep disturbances, 2) including HNC patients, 3) reporting the prevalence of sleep disturbances among HNC patients, and 4) full-text in English. Studies with all treatment modalities (surgery, radiotherapy, chemotherapy, combination, treatment with curative intent, or palliative treatment), phase of treatment (before, during, or after treatment), and any study design were included. Case-reports, narrative studies, study protocols, conference abstracts, editorials, and systematic reviews were excluded. The prevalence did not have to be the primary aim of the study.

Screening and selection of relevant articles

Two independent reviewers (Santoso AMM and Jansen F) each screened titles and abstracts after previously removing all duplicates from the search results. Titles and abstracts which were clearly not relevant (e.g., focusing on patients with benign tumors, non-adult populations, or animal studies) were excluded. Full-texts of the remaining references were retrieved. Subsequently, relevant full-texts were selected based on the inclusion and exclusion criteria. Disagreements were discussed and when necessary, a third reviewer (Verdonck-de Leeuw IM and/or van Straten A) was consulted until agreement was reached.

Data extraction and quality assessment

Both data extraction and quality assessment were performed by two independent reviewers (Santoso AMM and Jansen F). Any disagreements between raters were discussed and when necessary, a third reviewer (Verdonck-de Leeuw and/or van Straten A) was consulted until consensus was reached. We extracted information related to: study characteristics (i.e., publication year, country of study, study design, sample size, and eligibility criteria), population characteristics (i.e., demographics, cancer site and stage, and treatment characteristics), sleep disturbance measures (i.e., measurement instrument used and time point of measurement), and the prevalence of sleep disturbances (i.e., overall prevalence and prevalence among subgroups).

Each study was appraised for its methodological quality and potential bias. We used the critical appraisal checklist developed by the Joanna Briggs Institute [27]. In brief, this list consists of nine items examining the quality of studies which report prevalence, based on how the study was designed, conducted, and reported (Table 2, footnote). Each item is answered with yes, no, unclear (i.e., when some information is not reported in the article), or not applicable (i.e., when the question is not applicable to a certain study design). We calculated the total quality score for each study based on the total number of positively scored items. For the third item in this list ('Was the sample size adequate?'), we used a recommended formula to calculate minimum sample size in prevalence studies [28]. Using this formula, the minimum sample size was 289 participants [28, 29].

Analyses

Pooled means of prevalence rates were calculated using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood 2013). For each of the sleep disturbances, the pooled prevalence rate was calculated using a random effects model because it was expected that the studies would be methodologically heterogeneous [29]. Heterogeneity was visually examined by inspecting the forest plots and statistically confirmed by examining the I^2 values. An I^2 value of 0% indicates no observed heterogeneity among

studies, 1-25% indicates low heterogeneity, 25 - 75% indicates moderate heterogeneity, and >75% indicate high heterogeneity [30]. A confidence interval of 95% was used. We also examined the prevalence rate in a set of pre-defined groups, namely: type of treatment (surgery, chemotherapy, or (chemo-) radiotherapy; single therapy or multimodal therapy), phase of treatment (before, during, or after), measurement instrument used (i.e., among different types of questionnaire or different cut-offs), and studies with a high quality (risk of bias assessment ≥ 5 items evaluated positive). Funnel plots were generated to visually examine the presence of publication bias, which was then statistically tested by Egger's regression test and Begg-Mazumdar's rank correlation test. When publication bias seemed to be present (p-value < 0.05), Duval-Tweedie's trim-fill test was performed to calculate the adjusted pooled estimates. Reporting of meta-analyses was performed according to PRISMA guidelines (Appendix 2) [31].

Results

Inclusion of studies

The search resulted in 7,191 records (Figure 1). The majority of the records were excluded based on title and abstract screening. Full-texts were retrieved for the remaining 87 references. Of these 87 records, 26 articles fulfilled the eligibility criteria and three additional relevant full-texts were found during hand-searching. This resulted in 29 full-texts of accumulatively 2,315 HNC patients included in this review.

Characteristics of the included studies

The majority (72%) of these studies had a cross-sectional design [32-52]. The remaining studies had prospective observational [53] or retrospective design [54-58]. Most studies (59%) were conducted in the USA, Canada, or European countries [34, 35, 37, 39-41, 43, 45-48, 50, 52, 54, 57, 59, 60]. Twenty-one studies focused specifically on HNC patients [32, 34-36, 39-42, 44-46, 48, 50, 51, 53-56, 58-60], while eight studies focused on mixed cancer diagnoses but included a separate analysis among HNC patients. Nineteen studies (66%) primarily aimed to measure sleep disturbances [32-36, 41, 42, 44-48, 50, 51, 53, 55-57, 60], while the remaining studies aimed to measure various symptoms [37-39, 43, 49, 52, 54, 59], quality of life [40], or psychiatric disorders [58]. The majority of the studies included HNC patients of mixed or unspecified site [33-35, 37-39, 41, 43, 44, 46-50, 52, 54, 57-60] while the remaining included HNC patients of specific location, such as tongue [32, 40], larynx [42, 51], nasopharynx [53, 55, 56], and oropharynx [45]. About 33% [36] up to 93% [51] of the study population consists of male HNC patients, while the gender proportion was unknown among eight studies [33, 37, 38, 43, 47, 49, 52, 57].

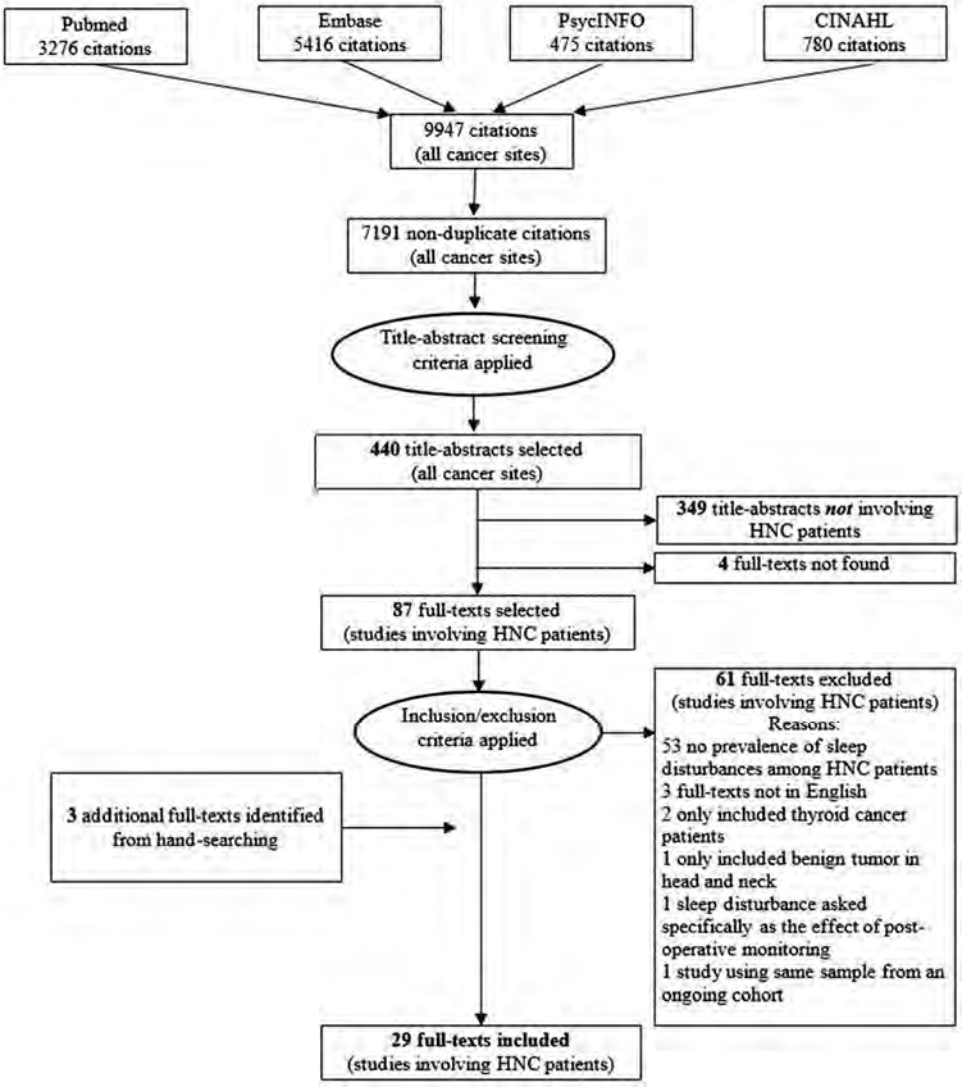

Figure 1 Flow diagram of the literature search and selection.

Among the 29 included studies, 10 studies (34%) measured more than one types of sleep disturbances [33, 34, 36, 39, 40, 44, 45, 50, 51, 59]. The included studies used a variety of definitions and instruments to report on sleep disturbances. The studies were grouped into three categories. The first category was insomnia and consisted of 17 studies [33, 34, 37, 39, 40, 43-45, 47, 49, 52, 54-59]. The studies used either self-reported insomnia symptoms (including poor sleep quality, disturbed sleep, and trouble falling asleep) as well as interview- and DSM-based insomnia diagnosis. Self-reported insomnia

symptoms were measured by questionnaires in 14 studies, of which four studies used the Pittsburgh sleep quality index (PSQI) with various cut-off scores [33, 34, 44, 55, 56], two studies used MD Anderson symptom inventory - head and neck module (MDASI-HN) [39, 59], two studies used the European organization for research and treatment of cancer (EORTC) questionnaire [43, 52], one study used the Hamilton depression inventory [47], and five studies used either a study-specific questionnaire or used a known questionnaire but did not report the cut-off score [33, 37, 40, 45, 49, 54].

One study used multiple definitions of self-reported insomnia symptoms (i.e., insomnia measured by insomnia severity index [ISI] with unknown cut-off and poor sleep quality measured by PSQI with cut-off of 5) [33]. The DSM-based diagnosis of insomnia was measured by structured interview in two studies [47, 57, 58].

The second category was hypersomnolence and consisted of 12 studies [33, 34, 36, 38-40, 44, 45, 49-51, 59]. Studies on excessive daytime sleepiness and drowsiness were included in this category. A slight majority of the studies (58%) used the Epworth sleepiness scale (ESS) to measure daytime sleepiness, although with various cut-offs or without pre-defined cut-off scores [33, 34, 36, 44, 45, 50, 51]. The remaining studies used various instruments to measure drowsiness, namely the MDASI-HN [39, 59], Edmonton symptom assessment scale [38, 49], or Memorial symptom assessment scale [40].

The third category was sleep-related breathing disturbances and consisted of 14 studies [32, 34-36, 41, 42, 44-46, 48, 50, 51, 53, 60]. We included studies on OSA and OSA-related symptoms into this category. Polysomnography (PSG) was used in the majority of studies (n=10, 71%) [32, 34-36, 42, 46, 48, 51, 53, 60] to establish the diagnoses, while three studies used home sleep testing [41, 45, 50]. Questionnaires and interviews were used to measure symptoms such as snoring and choking /gasping during sleep [44-46, 50].

We found no studies reporting on the prevalence of the remaining types of sleep disturbances, such as circadian rhythm sleep-wake disorder, parasomnia, or sleep-related movement disorders.

Three studies did not report details related to treatment phase [37, 38, 43]. Among the studies that provided details on treatment phase, three studies reported sleep disturbances before the start of treatment [39, 56, 60], two studies during treatment [33, 47], 12 studies after treatment [32, 35, 36, 40-42, 44-46, 48, 50, 51], five studies included patients who were either before or after treatment [53, 55, 57-59], and two studies reported sleep disturbances among patients who are undergoing treatment or who have finished their treatment [34, 52]. In general, these studies included patients with curative treatment, although not all studies provided detailed information on treatment intent. Three studies reported sleep disturbances during palliative treatment [49, 52, 54]. More details on the characteristics of the included studies are presented in Table 1.

Table 1 Overview of included studies (ordered alphabetically by first author's name)

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Chan MY et al., 2012[32]	Taiwan	Cross-sectional	Determine the prevalence of OSA in patients with primary squamous cell carcinoma of the tongue who underwent resection and/or RT.	Tongue	26	Mean 52 (32-71)	92	6 months to 11 years after treatment. Neck dissection 85%, RT 65%	OSA, PSG, AHI ≥ 5
Echchikhi Y et al., 2017[33]	Morocco	Cross-sectional	Determine prospectively the prevalence of sleep disorders, especially insomnia among patients with cancer receiving chemo and/or RT.	Unspecified*	41	Specific for HNC is not reported		Undergoing treatment. Surgery, chemo, RT and endocrine therapy.	Insomnia, ISI, cut-off unknown Poor sleep quality, PSQI ≥ 5 Sleepiness, ESS, cut-off unknown
Faiz SA et al., 2014[34]	USA	Cross sectional	Describe characteristics of sleep disorders in patients with HNC referred for evaluation based on PSG data; determine the risk factors and symptoms that suggest underlying sleep-related breathing disorder	Unspecified	56	60 (28 - 87)	77	<5 years after diagnosis or currently undergoing treatment 80%. Prior RT 79%	Poor sleep quality, PSQI > 8 OSA, PSG, AHI > 5 Sleepiness, ESS ≥ 10
Friedman M et al., 2001[35]	USA	Cross sectional	Identify incidence of OSA in patients with HNC treated by surgical resection and compare it with general population.	Tongue base, pharynx or supraglottic larynx	24	Mean 65 (39 -83)	88	After surgery 100%, received RT 42%	OSA, PSG, RDI>15

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Gilat H et al., 2013[36]	Israel	Cross-sectional	Evaluate quality of sleep and the rate of sleep-disordered breathing in patients treated for tongue cancer with radial forearm free flap reconstruction.	Tongue	15	Mean 57 (27-79)	33	Mean time from treatment completion (including postoperative therapy): 4.9 years (range 2-6 years). After surgery (tongue dissection and elective neck dissection) = 100%.	OSA, PSG, AHI>5 Sleepiness ESS ≥ 8
Grond S et al., 1993[54]	Germany	Prospective observational	Assess the causes and mechanisms of pain and to evaluate the efficacy and side effects of the pain relief among HNC patients.	Nose, paranasal sinuses, nasopharynx, oropharynx, salivary glands, hypopharynx, larynx or other sites of the head	167	58±11	70	Before pain treatment (100%). Undergone RT 80%, undergone surgery 63%, undergone chemo 41%, received no anticancer treatment 9%. Palliative anticancer treatment 32%, exhausted oncologic options/no benefit anticipated from further treatment 68%	Insomnia, unspecified computerized form to measure the frequency of symptoms.

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Grond S et al., 1994[37]	Germany	Cross-sectional	Evaluate the prevalence of 15 important symptoms and symptom groups in cancer of different sites.	Unspecified*	236	Specific for HNC is not reported		At time of referral to the pain clinic for treatment of "intractable" pain. Treatment phase for HNC subsample not reported, but the majority of all cancer patients is palliative.	Insomnia, unspecified questionnaire
Gunn GB et al., 2013[59]	USA	Cross-sectional**	Examine the pattern of symptoms experienced by patients with HNC before planned RT or CRT	Unspecified	270	Median 59 (SD 11.9)	76	Median days from last day chemo 21.6 (SD 25.3), from surgery to completion of MDASI-HN: 39.1 days (SD 25.7). Before starting curative RT-based treatment (100%). Prior chemo 26.7%, prior surgery 29%.	Disturbed sleep MDASI-HN ≥ 5 (moderate to severe) Drowsiness MDASI-HN ≥ 5 (moderate to severe)
Gupta M et al., 2016[38]	India	Cross-sectional	Assess presence and severity of various symptoms among critically ill cancer patients at the time of admission to an intensive care unit.	Unspecified*	26	Specific for HNC is not reported		Not reported	Drowsiness ESAS, cut-off unknown

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Hanna EY et al., 2015[39]	USA	Cross-sectional	Assess and explore symptom severity and interference in treatment-naive HNC patients.	Unspecified	748	Median 59 (SD 14.6)	68	Had no prior cancer therapy (100%)	Disturbed sleep MDASI-HN ≥ 5 (moderate to severe) Drowsiness MDASI-HN ≥ 5 (moderate to severe)
Harrison LB et al., 1997[40]	USA	Cross-sectional	Evaluate quality of life in patients treated with primary RT for cancer of the base of tongue.	Base of tongue	29	58 (35 - 71)	81	Median follow-up 5 years (min.3 years). After curative RT (100%),	Insomnia, MSAS, cut-off unknown Drowsiness, MSAS, cut-off unknown
Huyett P et al., 2017[41]	USA	Cross-sectional	Assess the prevalence of OSA in HNC patients treated with RT or CRT for laryngeal or oropharyngeal primary tumor sites.	Larynx or oropharynx	16	62 (48-75)	81	> 3 months after RT or CRT (100%), no active or recurrent disease	OSA, HST, AHI ≥ 5
Israel Y et al., 2006[42]	Brazil	Cross-sectional	Assess occurrence and severity of OSA in patients undergoing laryngectomy for the treatment of laryngeal carcinoma.	Larynx	22	Mean 66 (50 - 80)	91	Underwent laryngectomy in the last 6 years (100%)	OSA, PSG, AHI ≥ 15, moderate to severe
Johnsen AT et al., 2009[43]	Denmark	Cross-sectional	Measure symptoms and problems in advanced cancer patients and identify the predictors.	Unspecified*	72	Specific for HNC is not reported		Diagnosis/treatment information specific for HNC is not reported	Insomnia, EORTC-C30 ≥ 33.3

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Li N et al., 2017[44]	Japan	Cross-sectional	Provide a detailed description of the characteristics of sleep disturbance in long-term HNC survivors.	Unspecified	77	Mean 68 (28-86)	68	≥3 years after surgical treatment (100%)	Poor sleep quality, PSQI ≥ 5 and PSQI ≥ 8 Snoring, PSQI Sleepiness, ESS≥ 10
Lin HC et al., 2014[53]	Taiwan	Retrospective	Assess changes in respiratory sleep indexes, sleep architecture, and daytime somnolence before and after treatment in patients with nasopharyngeal cancer.	Nasopharynx	18	Mean 50	83	Before curative treatment (Chemo) RT=100%	OSA, PSG, AHI ≥ 5, AHI ≥ 15 (moderate or severe)
Loth A et al., 2017[45]	France	Cross-sectional	Evaluate the rate of OSA in a population of patients treated for an advanced oropharyngeal cancer.	Oropharynx	51	Mean 6 (44-76)	73	≥ 12 months post treatment. Combined chemo 80%, surgery and CRT 20%. Mean time between end of treatment and sleep disturbance measurement 54 months, (20 - 84 months)	Trouble falling asleep, sleep consultation OSA, HST AHI>10 Sleepiness, ESS ≥ 10
Mo YL et al., 2014[55]	China	Prospective observational	Explore cognitive function, and prevalence of depression, anxiety and sleep changes in nasopharyngeal carcinoma patients.	Nasopharynx	51	Mean 40 (24-60)	63	After diagnosis (before treatment started)=100%	Poor sleep quality, PSQI>5

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Nesse W et al., 2006[46]	The Netherlands	Cross-sectional	Identify the prevalence of OSA within a Dutch population of patients treated for HNC.	Oral or oropharynx	33	Mean 62 (38-87)	70	6-months to 5 year post curative treatment (100%). Surgery 39%, Surgery and RT 39%, RT 22%	OSA, PSG AHI ≥ 5 OSA-related complaints, ESS ≥ 10 or ≥ 2 study-specific items
Palesh OG et al., 2010[47]	USA	Cross-sectional	Determine prospectively the prevalence of insomnia among patients with cancer receiving chemo.	Unspecified*	4	Specific for HNC is not reported		Starting chemo (100%)	Clinical insomnia HDI, cut-off based on DSM-IV
Payne RJ et al., 2005[60]	Canada	Cross-sectional**	Determine the prevalence of OSA among patients with malignant tumors of the oral cavity and oropharynx prior to primary surgical resection.	Oral cavity or oropharynx	17	64± 2	82	Before surgery (100%), range 2 - 14 days	OSA, PSG AHI ≥ 15
Qian W et al., 2010[48]	Canada	Cross-sectional	Determine the point prevalence of sleep apnea in patients following oral and oropharyngeal cancer treatment	Oral or oropharynx	24	Mean age surgical group 64, nonsurgical group 55	67	≥ 6 months after completion primary treatment; no residual or recurrent disease (100%)	OSA PSG RDI ≥ 15 (moderate and severe) OSA PSG RDI ≥ 5 (all severity)
Qin L et al., 2015[56]	China	Prospective observational	Examine sleep and psychological characteristics in patients with local-advanced nasopharyngeal carcinoma following IMRT completion and concurrent chemo.	Nasopharynx	60	39.8±8.9	62	After diagnosis, before IMRT started (100%); (2 cycles concurrent chemo 33%, 3 cycles of concurrent therapy 67%)	Poor sleep quality, PSQI>5

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Savard J et al., 2011[57]	Canada	Prospective observational	Assess the prevalence and natural course of insomnia comorbid with cancer during an 18-month period in patients undergoing treatment for non-metastatic cancer.	Unspecified*	59	Specific for HNC is not reported		Before curative surgery (100%)	Insomnia symptoms, IIS based on DSM-IV criteria
Shao YJ et al., 2016[49]	China	Cross-sectional	To identify prevalence and severity of non-pain symptoms and to clarify possible influences on each non-pain symptom.	Unspecified*	14	Specific for HNC is not reported		Palliative 100%, immediately after admission to hospital	Insomnia, study-specific scale, cut-off unknown Drowsiness, ESAS, cut-off unknown
Steffen A et al., 2009[50]	Germany	Cross-sectional	Assess the prevalence of OSA in HNC patients following surgical treatment.	Unspecified	31	OSA patients 67 (59-77), non-OSA patients 64 (48-77)	71	Within 2 years of last aftercare visit, but more than 6 months after last surgical and/or adjuvant therapy.	OSA, HST AHI ≥ 20 snoring, interview Sleepiness, ESS ≥ 10
Teixeira RC et al., 2013[51]	Brazil	Cross-sectional	Compare the prevalence and severity of OSA in patients undergoing laryngectomy.	Larynx	14	68 (41-84)	93	After partial laryngectomy (100%), mean time after end of treatment 54 months (6 - 84 months)	OSA, PSG AHI 5-30 (mild) OSA, PSG AHI>30 (severe) OSA, PSG AHI>5 (all severity) Sleepiness, ESS>10

Table 1 continued.

Author, year	Country	Design	Primary aim	HNC site	n	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument and cut-off score
Unal D et al., 2016[58]	Turkey	Prospective observational	Evaluate the effects of RT on psychiatric disorder in HNC patients.	Unspecified	51	57.6 ± 11.2	90	Before RT	Sleep disorder, interview DSM-IV
van den Beuken-van Everdingen MH et al., 2009[52]	The Netherlands	Cross-sectional	To measure the prevalence of non-pain physical symptoms and psychological symptoms in patients with cancer.	Unspecified*	63	Specific for HNC is not reported		Curative 62% (of which 64% >6 months after treatment, 36% current/ ≤6 months after curative treatment); palliative 38%	Trouble sleeping EORTC-C30 score 3 (moderate) or 4 (severe)

Note:

Age was denoted in mean ± standard deviation (SD) or median (range), otherwise noted. All percentages are rounded.

* The study focused on mixed cancer patients. Sleep disturbances among head and neck cancer (HNC) patients were reported.

** Original study design is prospective observational, sleep analysis is performed at one study point (cross-sectional).

Abbreviations: AHI: apneaehypopnea index; Chemo: chemotherapy; CRT: chemoradiotherapy; DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition; EORTC: European organization for research and treatment of cancer; ESAS: Edmonton symptom assessment scale; ESS: Epworth sleepiness scale; HDI: Hamilton depression inventory; HNC: head and neck cancer; HST: home sleep test; IIS: insomnia interview schedule; IMRT: intensity modulated radiotherapy; ISI: insomnia severity index; MDASI-HN: MD Anderson symptom inventory e head and neck module; MSAS: Memorial symptom assessment scale; OSA: obstructive sleep apnea; PSG: polysomnography; PSQI: Pittsburgh sleep quality index; RDI: respiratory disturbance index; RT: radiotherapy; SD: standard deviation.

Quality and risk of bias assessment

The quality and risk of bias assessment is presented in Table 2. Only one study (3%) had a sufficient sample size (i.e., ≥289 participants) [39]. A majority of the studies (86%) had a sample size of less than 100 HNC patients [32-36, 38, 40-53, 55-58, 60]. Two studies (7%) scored positive on the item about response rate [39, 53]. The remaining studies scored negative as they had a response rate of less than 70% and did not report on the characteristics of non-responders versus responders, which hampers the ability to assess whether non-response might have affected the prevalence rate. Nineteen studies (66%) used validated sleep disturbance instruments or established diagnosis criteria of sleep disturbance [32, 33, 36, 38, 39, 41, 42, 44, 46, 48, 49, 51, 53, 55-60], while the remaining studies used either study-specific questionnaires or instruments not specifically validated to measure sleep disturbances. Seventeen studies (59%) performed appropriate statistical analysis [32, 35, 41, 42, 44-48, 50, 51, 53-55, 57, 58, 60] which is defined as providing correct prevalence rates including the total number of patients screened on sleep disturbances and the actual number of patients with sleep disturbances. On average, studies had three positively marked items, ranging from one [34] to five [39, 41, 52, 55, 56, 58, 59].

Table 2 Quality and risk of bias appraisal of included studies (ordered alphabetically by first author's name).

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total positive score
Chan MY et al., 2012[32]	**Y**	U	N	N	U	**Y**	U	**Y**	U	3
Echchikhi Y et al., 2017*[33]	N	**Y**	N	N	U	**Y**	**Y**	N	U	3
Faiz SA et al., 2014[34]	N	**Y**	N	N	U	U	N	N	N	1
Friedman M et al., 2001[35]	**Y**	N	N	N	U	U	U	**Y**	U	2
Gilat H et al., 2013[36]	**Y**	**Y**	N	**Y**	U	**Y**	U	N	U	4
Grond S et al., 1993[54]	**Y**	**Y**	N	N	U	U	U	**Y**	U	3
Grond S et al., 1994*[37]	**Y**	**Y**	N	U	U	U	U	N	U	2
Gunn GB et al., 2013[59]	**Y**	**Y**	N	**Y**	U	**Y**	**Y**	N	U	5
Gupta M et al., 2016*[38]	**Y**	U	N	U	U	**Y**	N	N	U	2
Hanna EY et al., 2015[39]	**Y**	U	**Y**	**Y**	**Y**	**Y**	U	N	NA	5
Harrison LB et al., 1997[40]	U	U	N	**Y**	U	U	**Y**	N	U	2
Huyett P et al., 2017[41]	**Y**	U	N	**Y**	U	**Y**	**Y**	**Y**	U	5
Israel Y et al., 2006[42]	**Y**	U	N	**Y**	U	**Y**	U	**Y**	N	4
Johnsen AT et al., 2009*[43]	**Y**	N	N	U	U	U	**Y**	N	N	2
Li N et al., 2017[44]	N	N	N	N	U	**Y**	U	**Y**	U	2
Lin HC et al., 2014[53]	N	U	N	N	**Y**	**Y**	**Y**	**Y**	NA	4
Loth A et al., 2017[45]	**Y**	**Y**	N	**Y**	U	U	U	**Y**	U	4
Mo YL et al., 2014[55]	N	U	N	**Y**	U	**Y**	**Y**	**Y**	**Y**	5

Table 2 continued.

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total positive score
Nesse W et al., 2006[46]	N	**Y**	N	**Y**	U	**Y**	U	**Y**	N	4
Palesh OG et al., 2010*[47]	**Y**	U	N	U	U	U	**Y**	**Y**	U	3
Payne RJ et al., 2005[60]	**Y**	N	N	N	U	**Y**	**Y**	**Y**	U	4
Qian W et al., 2010[48]	**Y**	U	N	**Y**	U	**Y**	U	**Y**	N	4
Qin L et al., 2015[56]	**Y**	**Y**	N	**Y**	U	**Y**	U	N	**Y**	5
Savard J et al., 2011*[57]	N	U	N	U	U	**Y**	**Y**	**Y**	U	3
Shao YJ et al., 2016*[49]	N	**Y**	N	N	U	**Y**	**Y**	N	U	3
Steffen A et al., 2009[50]	**Y**	**Y**	N	N	U	U	U	**Y**	U	3
Teixeira RC et al., 2013[51]	**Y**	**Y**	N	**Y**	U	**Y**	U	**Y**	N	5
Unal D et al., 2016[58]	**Y**	U	N	**Y**	U	**Y**	**Y**	**Y**	U	5
van den Beuken-van Everdingen MH et al., 2009*[52]	**Y**	U	N	U	U	U	**Y**	N	U	2

Note:

1. Q1-9: questions to assess study quality and risk of bias, as listed below.
   Q1: Was the sample frame appropriate to address the target population?
   Q2: Were study participants sampled in an appropriate way?
   Q3: Was the sample size adequate?
   Q4: Were the study subjects and the setting described in detail?
   Q5: Was the data analysis conducted with sufficient coverage of the identified sample?
   Q6: Were valid methods used for the identification of the condition?
   Q7: Was the condition measured in a standard, reliable way for all participants?
   Q8: Was there appropriate statistical analysis?
   Q9: Was the response rate adequate, and if not, was the low response rate managed appropriately?
2. Y, yes, highlighted ; N, no; U, unclear; NA, not applicable.
3. Studies marked with asterisk (*****) focused on mixed cancer patients, but sleep disturbances among head and neck cancer patients were reported. For these studies the items "Were the study subjects and the setting described in detail?" and "Was the data analysis conducted with sufficient coverage of the identified sample?" were scored as "Unclear".

Prevalence of insomnia

The pooled prevalence of insomnia was 29%, 45%, and 40% before, during, and after curative treatment, respectively (Table 3). During palliative care, the pooled prevalence is 52%. Before and after treatment, the prevalence of self-reported symptoms of insomnia was 30% and 46%, respectively, while the prevalence of a DSM-based diagnosis of insomnia disorder was 21% and 23%, respectively. When self-reported insomnia was defined with PSQI cut-off of 5, the pooled prevalence was 37% before and 75% after treatment. The comparison of pooled prevalence rates after different type of treatments was not possible since only two studies reported the prevalence rates after surgery only and one study reported the prevalence after chemotherapy only; the

remaining studies were performed among HNC patients after various combinations of treatment.

Table 3 Prevalence rates of insomnia

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	p-value
Before treatment, all [39, 55-59]	6	355/1093	0.29	0.20-0.41	86.16	36.12	<0.001
Study design							
• Good quality studies (≥5 positive items) [39, 55, 56, 58, 59]	5	326/1034	0.26	0.16-0.38	86.3	29.19	<0.001
Definition of insomnia							
• Self-reported insomnia, all [39, 55, 56, 59]	4	323/983	0.30	0.21-0.41	82.48	17.12	0.001
o Poor sleep quality: PSQI > 5 [55, 56]	2	41/111	0.37	0.29-0.46	0	0	1
o Disturbed sleep: MDASI-HN ≥ 5 [39, 59]	2	282/872	0.25	0.11-0.48	93.9	16.39	<0.001
• DSM-based diagnosis of insomnia [57, 58]	2	33/110	0.21	0.02-0.80	94.49	18.15	<0.001
During treatment, all [33, 47, 52]	3	26/59	0.45	0.33-0.58	0	1.39	0.500
Adjusted estimates (publication bias)[b]	NA	NA	0.50	0.38-0.61	NA	NA	NA
After treatment, all [40, 44, 45, 52, 55, 57-59]	8	168/395	0.40	0.24-0.58	89.35	65.73	<0.001
Study design							
• Good quality studies (≥5 positive items) [55, 58, 59]	3	50/173	0.25	0.05-0.67	94.81	38.50	<0.001
Definition of insomnia							
• Self-reported insomnia, all [40, 44, 45, 52, 55, 59]	6	144/304	0.46	0.28-0.65	88.86	44.89	<0.001
o PSQI ≥ 5 [44, 55]	2	97/128	0.75	0.54-0.89	80.92	5.24	0.022
• DSM-based diagnosis of insomnia [57, 58]	2	24/91	0.23	0.03-0.78	92.34	13.06	<0.001
Treatment type							
• Surgery only [57, 59]	2	33/114	0.31	0.09-0.67	94.81	38.5	0.004
• Single treatment[c, 55, 57, 59]	3	66/162	0.43	0.16-0.75	92.20	25.63	<0.001
Adjusted estimates (publication bias)[b]	NA	NA	0.47	0.28-0.66	NA	NA	NA

Table 3 continued.

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	p-value
Palliative care, all [49, 52]	2	16/38	0.52	0.04-0.97	92.32	13.02	<0.001
Unknown phase of treatment, all [37, 43]	2	182/308	0.54	0.34-0.73	89.79	9.80	0.002

Note:

a. Pooled estimate and 95%CI were analyzed using random effects model
b. Adjusted values generated using Duval-Tweedie's trim and fill test, random effects model
c. Single treatment including either surgery only or chemotherapy only

Abbreviations: CI, confidence interval; DSM, diagnostic and statistical manual of mental disorders; MDASI-HN, MD Anderson symptom inventory - head and neck module; NA, not applicable; PSQI, Pittsburgh sleep quality index

Table 4 Prevalence rates of hypersomnolence

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	p-value
Before treatment, all [39, 59]	2	177/872	0.16	0.07-0.32	88.78	8.91	0.003
After treatment, all [36, 40, 44, 45, 50, 51, 59]	7	90/275	0.32	0.20-0.48	80.40	30.61	<0.001
Study design							
• Good quality studies (≥ 5 positive items) [51, 59]	2	13/85	0.18	0.07-0.38	58.36	2.40	0.121
Definition of hypersomnolence							
• Sleepiness: ESS ≥ 10 [44, 45, 50, 51]	4	64/148	0.39	0.23-0.58	71.81	10.64	0.014
• Drowsiness [40, 59]	2	19/100	0.21	0.07-0.49	82.91	5.85	0.016
Treatment type							
• Surgery only [51, 59]	2	10/88	0.15	0.04-0.45	77.83	4.51	0.034
• Single treatment[b, 51, 59]	2	11/85	0.18	0.07-0.38	58.36	2.40	0.121

Note:

a. Pooled estimate and 95%CI were analyzed using random effects model
b. Single treatment including either surgery only, chemotherapy only or radiotherapy only.

Abbreviations: CI, confidence interval; ESS, Epworth sleepiness scale

Prevalence of hypersomnolence

The pooled prevalence of hypersomnolence was 16% before and 32% after curative treatment (Table 4). The prevalence rate of hypersomnolence during curative and palliative treatment was reported by each one study, which was 35% and 86%, respectively. When defined with ESS cut-off of 10, the pooled prevalence of sleepiness was 39%. The pooled prevalence of drowsiness measured by various instruments was 21%.

Prevalence of sleep-related breathing disturbances

The pooled prevalence of sleep-related breathing disturbances was 66% before and 51% after curative treatment (Table 5). No study reported the prevalence of sleep-related breathing disturbance during either curative or palliative treatment. After treatment, the pooled prevalence was 71% (apnea-hypopnea index [AHI] cut-off score of 5), 47% (AHI cut-off score of 15), and 37% (when defined as snoring). With respect to treatment modality, the pooled prevalence rate was 67% among patients who underwent surgery with (chemo-) radiotherapy, 58% among patients who underwent surgery alone, and 50% among patients who underwent chemoradiotherapy only.

Publication bias

Publication bias was examined on the prevalence of insomnia during treatment (p-value > 0.05), insomnia after treatment (p-value < 0.05), and sleep-related breathing disturbances after treatment (p-value < 0.05). Random effects model of Duval-Tweedie's test resulted in the adjusted pooled estimates of 50% for insomnia during treatment, 47% for insomnia after treatment, and 40% for sleep-related breathing disturbances after treatment (Table 3 and 5). We did not examine publication bias on the other sleep disturbances before and after treatment because the number of studies was too small (i.e., less than three studies).

Table 5 Prevalence rates of sleep-related breathing disturbances

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	p-value
Before treatment, all[b] [53, 60]	2	23/35	0.66	0.44-0.82	34.05	1.52	0.22
After treatment, all [32, 34-36, 41, 42, 44-46, 48, 50, 51, 53]	13	168/375	0.51	0.34-0.67	83.51	72.77	<0.001
Study design							
• OSA as exclusion criteria [32, 36, 41, 45, 48]	5	65/117	0.53	0.43-0.63	0	3.36	0.499
• Good quality studies (≥ 5 positive items) [41, 51]	2	21/30	0.76	0.20-0.98	79.87	4.97	0.026
Definition of sleep-related breathing disturbances							
• OSA: AHI ≥ 5 [32, 34, 36, 41, 42, 46, 48, 51, 53]	9	139/205	0.71	0.48-0.86	83.76	49.25	<0.001
• OSA: AHI ≥ 15 [35, 42, 48, 53]	4	37/68	0.47	0.34-0.61	56.42	6.89	0.076
• OSA: AHI ≥ 30 [42, 45, 51]	3	18/87	0.21	0.14-0.31	0	0.08	0.959
• Snoring [44, 45, 50]	3	57/159	0.37	0.09-0.77	94.97	39.77	<0.001
Treatment type							
• Surgery only [32, 35, 42, 48, 50, 51]	6	45/93	0.58	0.30-0.82	76.83	21.58	0.001
• Chemoradiotherapy only [48, 53]	2	14/27	0.50	0.33-0.76	47.82	1.92	0.166
• Surgery with (chemo)radiotherapy [32, 35, 48]	3	26/39	0.67	0.36-0.88	57.75	4.73	0.094
• Single treatment[c] [32, 34, 35, 42, 48, 50, 51]	7	84/137	0.65	0.37-0.85	81.48	32.4	<0.001
• Combination treatment[d] [32, 35, 45, 48, 53]	5	60/167	0.54	0.41-0.67	23.2	5.21	0.267
Adjusted estimates (publication bias)[e]	NA	NA	0.40	0.24-0.60	NA	NA	NA

Note:

a. Pooled estimate and 95% CI were analyzed using random effects model
b. Pooled prevalence of OSA defined with AHI ≥ 15
c. Single treatment including either surgery only, chemotherapy only or radiotherapy only.
d. Combination treatment including chemoradiotherapy (with or without other modality) and surgery with either chemotherapy or chemoradiotherapy.
e. Adjusted values generated using Duval-Tweedie's trim and fill test, random effects model

Abbreviations: AHI, apnea-hypopnea index; CI, confidence interval; OSA, obstructive sleep apnea; NA, not applicable

Discussion

In this systematic review and meta-analysis investigating the prevalence of sleep disturbances among HNC patients, we found 29 studies measuring three types of sleep disturbances: insomnia, hypersomnolence, and sleep-related breathing disturbances. No studies were found investigating circadian rhythm sleep-wake disorders, parasomnias, or sleep-related movement disorders, despite our extensive search strategy. The pooled prevalence of insomnia was 29% before treatment, 45% during treatment (50% after correcting for publication bias), and 40% after treatment (47% after correcting for publication bias). The pooled prevalence of hypersomnolence was 16% before and 32% after treatment. For sleep-related breathing disturbances, the pooled prevalence was 66% before and 51% after treatment (40% after correcting for publication bias). Only one study reported the prevalence of HNC patients who had both sleep-related breathing disturbance and hypersomnolence[45], hence we were unable to confirm whether the prevalence rate of hypersomnolence overlaps with that of sleep-related breathing disturbance.

The prevalence of sleep disturbances before the start of HNC treatment (16-66%) is notably higher compared to that of the general population (2-38%) [61, 62]. Tumor mass effect of HNC may cause obstruction around tongue, pharynx, and epiglottis, the most common sites involved in OSA [63]. In addition, anxiety and depression are highly prevalent at the time of HNC diagnosis [8, 9] which may also contribute to insomnia. People recently confronted with the diagnosis of HNC may experience fear and uncertainty related with HNC treatment and its outcome [64]. Such uncertainty may affect their social situations and sleep-wake patterns. Furthermore, two major risk factors of HNC, alcohol abuse and tobacco smoking, might play a role in the high prevalence of sleeping disturbances among HNC patients. Heavy alcohol users often experience insomnia even after they stop their alcohol consumption [65], while smokers suffer more insufficient sleep compared to non-smokers [66]. Moreover, smoking damages oropharyngeal mucosal structure [67] and this may contribute to the relationship of smoking with sleep-related breathing disturbances in patients with HNC.

The evidence on the high prevalence of sleep disturbances during treatment was based on only two studies investigating insomnia [49, 52] and one study investigating hypersomnolence [33], with pooled prevalence of 45% and 35%, respectively. Cancer treatment is physically and psychologically burdensome for HNC patients due to the treatment-related side-effects. HNC patients who are undergoing (chemo-) radiotherapy often experience mucositis-related symptoms such as xerostomia and oral pain, as well as fatigue, drowsiness, and nausea [7, 68]. These symptoms may cause circadian rhythm changes among HNC patients and may contribute to the high prevalence of insomnia and hypersomnolence during treatment. Moreover, one out of five HNC patients continues smoking or drinking alcohol during cancer treatment [69]

which may worsen their sleep problems. Pain-relievers such as opioids are also often prescribed during cancer treatment and may result in sleep-wake rhythm changes [16, 17]. So far, however, only a limited number of studies reported on the prevalence of sleep disturbances during HNC treatment, therefore warranting additional studies.

The prevalence rates of sleep disturbances after treatment were also high: 40%, 32%, and 51% on insomnia, hypersomnolence, and sleep-related breathing disturbances, respectively. This might be related to HNC symptoms such as dry mouth complaints, lymphedema in the head and neck area, tinnitus, and dysregulation of thyroid hormone after (chemo-) radiotherapy. The high prevalence of insomnia may be associated with psychological symptoms such as depression, post-traumatic stress disorders, problems with body-image, and fear of cancer recurrence. These symptoms may continue to be present after HNC is treated successfully [64, 70-73]. In addition, radiation in the head and neck area may be associated with sleep-related breathing disturbances in two ways: first, it may alleviate breathing disturbances by reducing the tumor mass; and on the other hand, it may cause scarring, airway narrowing, and alterations of the sensory- and mechanoreceptors in the upper airway [63].

We also found that more than a half of HNC patients receiving palliative care reported insomnia. This high prevalence of insomnia among patients in palliative care may be explained by the above-mentioned causes of sleep disturbances before, during, and after treatment of HNC, and further worsened by the advanced stage of cancer, cancer recurrence, distant metastasis or presence of a second primary cancer [73]. In addition, palliative care patients report high level of anxiety [49], which affects sleep quality.

The strength of this study is that meta-analytic methods were used to investigate the prevalence of various types of sleep disturbances among HNC patients. We also presented prevalence rates of sleep disturbances in different phases of treatment (i.e., before, during, and after treatment) and palliative care, which resulted in a thorough overview of studies performed so far.

We, however, also acknowledge some limitations of this study. Considerable heterogeneity was found regarding the definition of sleep disturbances, the used measurement instruments to assess sleep disturbances as well as the used cut-off scores on the measurement instruments. This heterogeneity was in line with previous reviews on the prevalence of sleep disturbances among mixed cancer patients and the general population [29, 61]. In addition, only a limited number of studies were performed per subgroup of patients (e.g., regarding phase of treatment or type of treatment), which hindered the ability to statistically compare prevalence rates among these subgroups, as well as to examine differences among countries and study years. For example, it seems that among HNC patients, sleep-related breathing disturbances are more frequently present than other types of sleep disturbances but this observation

needs further investigation. Also, we were only able to report the prevalence of hypersomnolence as a symptom, as there is lack of studies which reported hypersomnolence as a sleep disorder. Sleep disturbances, additionally, seem to increase after treatment, but longitudinal studies investigating the course of sleep disturbances from diagnosis to follow-up are needed to confirm this observation. Another limitation is that publication bias is likely to have occurred, which may either under- or overestimate the reported prevalence rates in this meta-analysis. We also excluded non-English articles, which may have resulted in underrepresentation of prevalence rates of sleep disturbances in non-English-speaking countries. Finally, most studies were of insufficient methodological quality: a small group of HNC patients were often included in the study, inadequate information on their participant recruitment were often provided, and non-validated instruments were often used to measure sleep disturbances.

Conclusion

This systematic review and meta-analysis demonstrated that sleep disturbances are highly prevalent at all HNC treatment phases, underlining the importance of early screening and tailored intervention for sleep disturbance among HNC patients. Further studies are essential to investigate the course of sleep disturbances from diagnosis to follow-up among both cancer survivors and patients in palliative care. Also, more insight is needed to understand the clinical, psychological, and life-style related factors associated with prevalence rates among different subgroups of HNC patients.

References

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA oncology. 2017;3(4):524-48.
2. Duffy SA, Khan MJ, Ronis DL, Fowler KE, Gruber SB, Wolf GT, et al. Health behaviors of head and neck cancer patients the first year after diagnosis. Head Neck. 2008;30(1):93-102.
3. Mia H, Paul B, Simone B, Xavier C, Chu C, Maria Paula C, et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. JNCI Journal of the National Cancer Institute [Internet]. 2007; 99(10):[777-89 pp.].
4. McNamara JP, Wang J, Holiday DB, Warren JY, Paradoa M, Balkhi AM, et al. Sleep disturbances associated with cigarette smoking. Psychology, health & medicine. 2014;19(4):410-9.
5. Ebrahim IO, Shapiro CM, Williams AJ, Fenwick PB. Alcohol and sleep I: effects on normal sleep. Alcohol Clin Exp Res. 2013;37(4):539-49.
6. Rosenthal DI, Mendoza TR, Fuller CD, Hutcheson KA, Wang XS, Hanna EY, et al. Patterns of symptom burden during radiotherapy or concurrent chemoradiotherapy for head and neck cancer: a prospective analysis using the University of Texas MD Anderson Cancer Center Symptom Inventory-Head and Neck Module. Cancer. 2014;120(13):1975-84.
7. Shuman AG, Duffy SA, Ronis DL, Garetz SL, McLean SA, Fowler KE, et al. Predictors of poor sleep quality among head and neck cancer patients. Laryngoscope. 2010;120(6):1166-72.
8. Shepherd KL, Fisher SE. Prospective evaluation of quality of life in patients with oral and oropharyngeal cancer: from diagnosis to three months post-treatment. Oral Oncol. 2004;40(7):751-7.
9. Krebber AM, Jansen F, Cuijpers P, Leemans CR, Verdonck-de Leeuw IM. Screening for psychological distress in follow-up care to identify head and neck cancer patients with untreated distress. Support Care Cancer. 2016;24(6):2541-8.
10. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of Insomnia, Depression, and Anxiety. Sleep. 2005;28(11):1457-64.
11. American Academy of Sleep M. International classification of sleep disorders. Third edition. ed. Darien, IL: American Academy of Sleep Medicine; 2014.
12. Abad VC, Guilleminault C. Diagnosis and treatment of sleep disorders: a brief review for clinicians. Dialogues in Clinical Neuroscience. 2003;5(4):371-88.
13. Ohayon MM, Reynolds CF. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Medicine. 2009;10(9):952-60.
14. Induru RR, Walsh D. Cancer-related insomnia. The American journal of hospice & palliative care. 2014;31(7):777-85.
15. Gibbins J, McCoubrie R, Kendrick AH, Senior-Smith G, Davies AN, Hanks GW. Sleep-wake disturbances in patients with advanced cancer and their family carers. J Pain Symptom Manage. 2009;38(6):860-70.
16. Sethi RV, Panth N, Puram SV, Varvares MA. Opioid prescription patterns among patients with head and neck cancer. JAMA Otolaryngology–Head & Neck Surgery. 2018;144(4):382-3.
17. Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis. 2012;4(6):608-16.
18. Hickok JT, Morrow GR, Roscoe JA, Mustian K, Okunieff P. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. Journal of Pain & Symptom Management. 2005;30(5):433-42.

19. López E, de la Torre-Luque A, Lazo A, Álvarez J, Buela-Casal G. Assessment of sleep disturbances in patients with cancer: Cross-sectional study in a radiotherapy department. European Journal of Oncology Nursing. 2016;20:71-6.
20. Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. Nature and science of sleep. 2018;10:21-34.
21. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. Sleep medicine reviews. 2004;8(3):199-212.
22. Rada R. Obstructive sleep apnea and head and neck neoplasms. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2005;132(5):794-9.
23. Zhou J, Jolly S. Obstructive sleep apnea and fatigue in head and neck cancer patients. American journal of clinical oncology. 2015;38(4):411-4.
24. Ruel S, Savard J, Ivers H. Insomnia and self-reported infections in cancer patients: An 18-month longitudinal study. Health Psychology. 2015;34(10):983-91.
25. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. Social Science & Medicine. 2002;54(9):1309-21.
26. A systematic review on the prevalence of sleep disturbances among cancer patients [Internet]. PROSPERO. 2018 [cited 17 October 2018]. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088119.
27. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag. 2014;3(3):123-8.
28. Naing L, Winn T, Rusli B. Practical issues in calculating the sample size for prevalence studies. Archives of orofacial Sciences. 2006;1:9-14.
29. Otte JL, Carpenter JS, Manchanda S, Rand KL, Skaar TC, Weaver M, et al. Systematic review of sleep disorders in cancer patients: can the prevalence of sleep disorders be ascertained? Cancer medicine. 2015;4(2):183-200.
30. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.
31. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
32. Chan M-Y, Chou M-Y, Lee L-T, Cheng C-S, Hsiao Y-L, Wong Y-K. Prevalence of obstructive sleep apnea in patients with squamous cell carcinoma of the tongue following ablation surgery. Journal of Dental Sciences. 2012;7(3):245-9.
33. Echchikhi Y, El-Abbassi S, Touil A, Kacemi H, El-Majjaoui S, Kebdani T, et al. Sleep Disorders and Sleep Quality in Moroccan Adult Patients with Cancer during Treatment. Journal of Cancer Science & Therapy. 2017;9:9.
34. Faiz SA, Balachandran D, Hessel AC, Lei X, Beadle BM, William WN, Jr., et al. Sleep-related breathing disorders in patients with tumors in the head and neck region. Oncologist. 2014;19(11):1200-6.
35. Friedman M, Landsberg R, Pryor S, Syed Z, Ibrahim H, Caldarelli DD. The occurrence of sleep-disordered breathing among patients with head and neck cancer. The Laryngoscope. 2001;111(11):1917-9.
36. Gilat H, Shpitzer T, Guttman D, Soudry E, Feinmesser R, Bachar G. Obstructive sleep apnea after radial forearm free flap reconstruction of the oral tongue. Laryngoscope. 2013;123(12):3223-6.
37. Grond S, Zech D, Diefenbach C, Bischoff A. Prevalence and pattern of symptoms in patients with cancer pain: a prospective evaluation of 1635 cancer patients referred to a pain clinic. Journal of pain and symptom management. 1994;9(6):372-82.
38. Gupta M, Sahi MS, Bhargava A, Talwar V. A prospective evaluation of symptom prevalence and overall symptom burden among cohort of critically ill cancer patients. Indian journal of palliative care. 2016;22(2):118.

39. Hanna EY, Mendoza TR, Rosenthal DI, Gunn GB, Sehra P, Yucel E, et al. The symptom burden of treatment-naive patients with head and neck cancer. Cancer. 2015;121(5):766-73.
40. Harrison LB, Zelefsky MJ, Pfister DG, Carper E, Raben A, Kraus DH, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 1997;19(3):169-75.
41. Huyett P, Kim S, Johnson JT, Soose RJ. Obstructive sleep apnea in the irradiated head and neck cancer patient. Laryngoscope. 2017;127(11):2673-7.
42. Israel Y, Cervantes O, Abrahão M, Ceccon FP, Filho MFM, Nascimento LA, et al. Obstructive sleep apnea in patients undergoing supracricoid horizontal or frontolateral vertical partial laryngectomy. Otolaryngology—Head and Neck Surgery. 2006;135(6):911-6.
43. Johnsen AT, Petersen MA, Pedersen L, Groenvold M. Symptoms and problems in a nationally representative sample of advanced cancer patients. Palliative medicine. 2009;23(6):491-501.
44. Li N, Otomaru T, Taniguchi H. Sleep quality in long-term survivors of head and neck cancer: preliminary findings. Support Care Cancer. 2017;25(12):3741-8.
45. Loth A, Michel J, Giorgi R, Santini L, Rey M, Elbaum JM, et al. Prevalence of obstructive sleep apnoea syndrome following oropharyngeal cancer treatment: A prospective cohort study. Clin Otolaryngol. 2017;42(6):1281-8.
46. Nesse W, Hoekema A, Stegenga B, van der Hoeven JH, de Bont LG, Roodenburg JL. Prevalence of obstructive sleep apnoea following head and neck cancer treatment: a cross-sectional study. Oral Oncol. 2006;42(1):108-14.
47. Palesh OG, Roscoe JA, Mustian KM, Roth T, Savard J, Ancoli-Israel S, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol. 2010;28(2):292-8.
48. Qian W, Haight J, Poon I, Enepekides D, Higgins KM. Sleep apnea in patients with oral cavity and oropharyngeal cancer after surgery and chemoradiation therapy. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010;143(2):248-52.
49. Shao YJ, Ji K, Hao JL, Cheng XJ, Guan BQ, Liu WS, et al. Nonpain Symptom Prevalence and Intensity of Inpatients With Moderate to Severe Cancer Pain in China. The American journal of hospice & palliative care. 2016;33(5):448-55.
50. Steffen A, Graefe H, Gehrking E, Konig IR, Wollenberg B. Sleep apnoea in patients after treatment of head neck cancer. Acta Otolaryngol. 2009;129(11):1300-5.
51. Teixeira RC, Cahali MB. Obstructive sleep apnea: is there a difference between vertical and horizontal laryngectomy? Braz J Otorhinolaryngol. 2013;79(6):668-72.
52. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Quality of life and non-pain symptoms in patients with cancer. J Pain Symptom Manage. 2009;38(2):216-33.
53. Lin HC, Friedman M, Chang HW, Fang FM, Lin MC, Su MC. Impact of head and neck radiotherapy for patients with nasopharyngeal carcinoma on sleep-related breathing disorders. JAMA Otolaryngol Head Neck Surg. 2014;140(12):1166-72.
54. Grond S, Diefenbach C, Zech D, Schug SA, Lynch J, Lehmann KA. Validation of World Health Organization guidelines for pain relief in head and neck cancer: a prospective study. Annals of Otology, Rhinology & Laryngology. 1993;102(5):342-8.
55. Mo YL, Li L, Qin L, Zhu XD, Qu S, Liang X, et al. Cognitive function, mood, and sleep quality in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer: a prospective study. Psychooncology. 2014;23(10):1185-91.
56. Qin L, Mo Y-L, Li L, Wei Z-J, Zhu X-D, Yin X, et al. Sleep characteristics and psychological symptoms in patients with locally advanced nasopharyngeal carcinoma before and after intensity-modulated radiotherapy and concurrent chemotherapy. Psychology, health & medicine. 2015;20(6):662-9.

57. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol. 2011;29(26):3580-6.
58. Unal D, Orhan O, Ozsoy SD, Besirli A, Eroglu C, Kaplan B. Effect of radiotherapy on psychiatric disorder in patients with head and neck cancer. Indian J Cancer. 2016;53(1):162-5.
59. Gunn GB, Mendoza TR, Fuller CD, Gning I, Frank SJ, Beadle BM, et al. High symptom burden prior to radiation therapy for head and neck cancer: a patient-reported outcomes study. Head Neck. 2013;35(10):1490-8.
60. Payne RJ, Hier MP, Kost KM, Black MJ, Zeitouni AG, Frenkiel S, et al. High prevalence of obstructive sleep apnea among patients with head and neck cancer. Journal of otolaryngology. 2005;34(5).
61. Partinen M. Epidemiology of sleep disorders. Handbook of clinical neurology. 2011;98:275-314.
62. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep medicine reviews. 2017;34:70-81.
63. Dedhia RC, Rosen CA, Soose RJ. What is the role of the larynx in adult obstructive sleep apnea? The Laryngoscope. 2014;124(4):1029-34.
64. Stout RA, Beckman NJ, Shelby SR, Labott SM. Psychological Issues in Head and Neck Cancer. Head & Neck Cancer: Current Perspectives, Advances, and Challenges: Dordrecht : Springer Netherlands : Springer; 2013. p. 751-800.
65. Brower KJ. Alcohol's effects on sleep in alcoholics. Alcohol research & health: the journal of the National Institute on Alcohol Abuse and Alcoholism. 2001;25(2):110.
66. Sabanayagam C, Shankar A. The association between active smoking, smokeless tobacco, secondhand smoke exposure and insufficient sleep. Sleep medicine. 2011;12(1):7-11.
67. Kim KS, Kim JH, Park SY, Won H-R, Lee H-J, Yang HS, et al. Smoking Induces Oropharyngeal Narrowing and Increases the Severity of Obstructive Sleep Apnea Syndrome. Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine. 2012;8(4):367-74.
68. Hanna E, Alexiou M, Morgan J, Badley J, Maddox AM, Penagaricano J, et al. Intensive chemoradiotherapy as a primary treatment for organ preservation in patients with advanced cancer of the head and neck: efficacy, toxic effects, and limitations. Archives of otolaryngology–head & neck surgery. 2004;130(7):861-7.
69. McCarter K, Baker AL, Britton B, Wolfenden L, Wratten C, Bauer J, et al. Smoking, drinking, and depression: comorbidity in head and neck cancer patients undergoing radiotherapy. Cancer medicine. 2018.
70. Howren MB, Christensen AJ, Karnell LH, Funk GF. Psychological Factors Associated With Head and Neck Cancer Treatment and Survivorship: Evidence and Opportunities for Behavioral Medicine. JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY. 2013;81(2):299-317.
71. Peach MS, Trifiletti DM, Vachani C, Arnold-Korzeniowski K, Bach C, Hampshire M, et al. Patient-reported outcomes in head and neck cancer: prospective multi-institutional patient-reported toxicity. Patient Related Outcome Measures. 2018;9:245.
72. Goepfert RP, Fuller CD, Gunn GB, Hanna EY, Lewin JS, Zaveri JS, et al. Symptom burden as a driver of decisional regret in long-term oropharyngeal carcinoma survivors. Head Neck. 2017;39(11):2151-8.
73. Schlieve T, Kolokythas A. Complications from Surgical Treatment of Oral Cancer. In: Radosevich JA, editor. Head & Neck Cancer: Current Perspectives, Advances, and Challenges. Dordrecht: Springer Netherlands; 2013. p. 721-49.

Appendix 1. Search strategy

PubMed

1. "Sleep Wake Disorders"[Mesh] OR (("Sleep"[Mesh] OR sleep*[tiab] OR wake[tiab] OR awake[tiab] OR waking[tiab] OR awaking[tiab] OR somnolence*[tiab] OR Somnolescent[tiab] OR REM[tiab] OR Circadian rhythm[tiab]) AND (disorder*[tiab] OR disturb*[tiab] OR paroxysmal[tiab])) OR dyssomnia*[tiab] OR Sleep problem*[tiab] OR Sleep difficult*[tiab] OR Sleep Deprivation*[tiab] OR Sleep Fragmentation*[tiab] OR Insufficient Sleep Syndrome*[tiab] OR Nyctohemeral Rhythm*[tiab] OR Sleep Phase Syndrome*[tiab] OR jet lag*[tiab] OR hypersomnolence*[tiab] OR hypersomnolence*[tiab] OR hypersomnia*[tiab] OR hypersomnia*[tiab] OR Kleine-Levin[tiab] OR narcoleps*[tiab] OR cataplex*[tiab] OR Gelineau*[tiab] OR nocturnal myoclonus syndrome*[tiab] OR ((Leg Movement*[tiab] OR Limb Movement*[tiab]) AND Sleep*[tiab]) OR restless leg*[tiab] OR Willis Ekbom[tiab] OR Wittmaack Ekbom[tiab] OR sleep apnea*[tiab] OR nocturnal apnea*[tiab] OR sleep hypopnea*[tiab] OR sleep apnoea*[tiab] OR nocturnal apnoea*[tiab] OR sleep hypopnoea*[tiab] OR sleep- disordered breathing[tiab] OR insomnia*[tiab] OR parasomnia*[tiab] OR Nocturnal Dystonia*[tiab] OR Sleep paralys*[tiab] OR Night Terror*[tiab] OR Pavor Nocturnus[tiab] OR Somnambulis*[tiab] OR Sleepwalking[tiab] OR Sleep walking[tiab] OR Nocturnal Wandering*[tiab] OR Jactatio Capitis Nocturna[tiab] OR Nocturnal Leg Cramp*[tiab] OR Sleep talking[tiab] OR Sleep start*[tiab] OR (((periodic[tiab] OR repetitive[tiab]) AND movement*[tiab]) AND sleep*[tiab]) OR plms[tiab] OR plmd[tiab]
2. "Neoplasms"[Mesh] OR cancer[sb] OR adenoma*[tw] OR anticarcinogen*[tw] OR blastoma*[tw] OR cancer*[tw] OR carcinogen*[tw] OR carcinom*[tw] OR carcinosarcoma*[tw] OR chordoma*[tw] OR germinoma*[tw] OR gonadoblastoma*[tw] OR hepatoblastoma*[tw] OR hodgkin disease[tw] OR hodgkin's disease[tw] OR hodgkins disease[tw] OR leukemi*[tw] OR lymphangioma*[tw] OR lymphangiomyoma*[tw] OR lymphangiosarcoma*[tw] OR lymphom*[tw] OR malignan*[tw] OR melanom*[tw] OR meningioma*[tw] OR mesenchymoma*[tw] OR mesonephroma*[tw] OR metasta*[tw] OR neoplas*[tw] OR neuroma*[tw] OR nsclc[tw] OR oncogen*[tw] OR oncolog*[tw] OR paraneoplastic[tw] OR plasmacytoma*[tw] OR precancerous[tw] OR sarcoma*[tw] OR teratocarcinoma*[tw] OR teratoma*[tw] OR tumor*[tw] OR tumour*[tw]
3. "Cohort Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Observational Studies as Topic"[Mesh] OR prospectiv*[tiab] OR cohort*[tiab] OR prevalen*[tiab] OR incidenc*[tiab] OR cross-sectional[tiab] OR crosssectional[tiab] OR observation*[tiab] OR longitudinal[tiab] OR epidemiol*[tiab]
4. 1 AND 2 AND 3

Limitations: Studies involving human participants
Date of search: 24 November 2017
Result: 3,276 articles found

PsycINFO

1. DE "Sleep Disorders" OR DE "Hypersomnia" OR DE "Insomnia" OR DE "Kleine Levin Syndrome" OR DE "Narcolepsy" OR DE "Parasomnias" OR DE "Sleepwalking" OR ((DE "Sleep" OR DE "Napping" OR DE "NREM Sleep" OR DE "REM Sleep" OR TI (sleep* OR wake OR awake ORwaking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm") OR AB (sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm")) AND (TI (disorder* OR disturb* OR paroxysmal) OR AB (disorder* OR disturb* OR paroxysmal))) OR TI ("Sleep problem*" OR "Sleep difficult*" OR
   "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR

"hypersomnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd) OR AB (((sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm") and (disorder* OR disturb* OR paroxysmal)) OR "Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient

Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hypersomnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd) OR AB ("Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hyper-somnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd) OR AB (((sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm") and (disorder* OR disturb* OR paroxysmal)) OR "Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hyper-somnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd)

2. DE "Neoplasms" OR DE "Benign Neoplasms" OR DE "Breast Neoplasms" OR DE "Endocrine Neoplasms" OR DE "Leukemias" OR DE "Melanoma" OR DE "Metastasis" OR DE "NervousSystem Neoplasms" OR DE "Terminal Cancer" OR DE "Brain Neoplasms" OR DE "Glioma" OR TI

(adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* OR germinoma* OR gonadoblastoma* OR hepatoblastoma* OR "hodgkin disease" OR "hodgkin s disease" OR "hodgkins disease" OR leukemi* OR lymphangioma* OR lymphangiomyoma* OR lymphangiosarcoma* OR lymphom* OR malignan* OR melanom* OR meningioma* OR mesenchymoma* OR mesonephroma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*) OR AB (adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* OR germinoma* OR gonadoblastoma* OR hepatoblastoma* OR "hodgkin disease" OR "hodgkin s disease" OR "hodgkins disease" OR leukemi* OR lymphangioma* OR lymphangiomyoma* OR lymphangiosarcoma* OR lymphom* OR malignan* OR melanom* OR meningioma* OR mesenchymoma* OR mesonephroma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*)

3. DE "Cohort Analysis" OR DE "Prospective Studies" OR DE "Longitudinal Studies" OR TI (prospectiv* OR cohort* OR prevalen* OR incidenc* OR "cross-sectional" OR crosssectional OR
4. observation* OR longitudinal OR epidemiol*) OR AB (prospectiv* OR cohort* OR prevalen* OR incidenc* OR "cross-sectional" OR crosssectional OR observation* OR longitudinal OR epidemiol*)
5. 1 AND 2 AND 3

Limitations: Studies involving human participants
Date of search: 23 November 2017
Result: 475 articles found

CINAHL

1. (MH "Sleep Disorders+") OR (((MH "Sleep+") OR TI (sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm") OR AB (sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm")) AND (TI (disorder* OR disturb* OR paroxysmal) OR AB (disorder* OR disturb* OR paroxysmal))) OR TI ("Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR"Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hypersomnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" ORinsomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd) OR AB (((sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm") and (disorder* OR disturb* OR paroxysmal)) OR "Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hypersomnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom"

OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd) OR AB ("Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hyper-somnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* ORGelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd) OR AB (((sleep* OR wake OR awake OR waking OR awaking OR somnolence* OR somnolescent OR REM OR "Circadian rhythm") and (disorder* OR disturb* OR paroxysmal)) OR "Sleep problem*" OR "Sleep difficult*" OR "Sleep Deprivation*" OR "Sleep Fragmentation*" OR "Insufficient Sleep Syndrome*" OR "Nyctohemeral Rhythm*" OR "Sleep Phase Syndrome*" OR "jet lag*" OR hypersomnolence* OR "hyper-somnolence*" OR hypersomnia* OR "hyper-somnia*" OR "Kleine-Levin" OR narcoleps* OR cataplex* OR Gelineau* OR "nocturnal myoclonus syndrome*" OR (("Leg Movement*" OR "Limb Movement*") and sleep*) OR "restless leg*" OR "Willis Ekbom" OR "Wittmaack Ekbom" OR "sleep apnea*" OR "nocturnal apnea*" OR "sleep hypopnea*" OR "sleep apnoea*" OR "nocturnal apnoea*" OR "sleep hypopnoea*" OR "sleep-disordered breathing" OR insomnia* OR parasomnia* OR "Nocturnal Dystonia*" OR "Sleep paralys*" OR "Night Terror*" OR "Pavor Nocturnus" OR Somnambulis* OR Sleepwalking OR "Sleep walking" OR "Nocturnal Wandering*" OR "Jactatio Capitis Nocturna" OR "Nocturnal Leg Cramp*" OR "Sleep talking" OR "Sleep start*" OR ((periodic OR repetitive) and movement* and sleep*) OR plms OR plmd)

2. (MH "Neoplasms+") OR TI (adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* OR germinoma* OR gonadoblastoma* OR hepatoblastoma* OR "hodgkin disease" OR "hodgkin s disease" OR "hodgkins disease" OR leukemi* OR lymphangioma* OR lymphangiomyoma* OR lymphangiosarcoma* OR lymphom* OR malignan* OR melanom* OR meningioma* OR mesenchymoma* OR mesonephroma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*) OR AB (adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* ORcarcinosarcoma* OR chordoma* OR germinoma* OR gonadoblastoma* OR hepatoblastoma* OR "Hodgkin disease" OR "hodgkin s disease" OR "hodgkins disease" OR leukemi* OR lymphangioma* OR lymphangiomyoma* OR lymphangiosarcoma* OR lymphom* OR malignan* OR melanom* OR meningioma* OR mesenchymoma* OR mesonephroma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*)
3. (MH "Nonexperimental Studies+") OR TI (prospectiv* OR cohort* OR prevalen* OR incidenc* OR cross-sectional" OR crosssectional OR observation* OR longitudinal OR epidemiol*) OR AB (prospectiv* OR cohort* OR prevalen* OR incidenc* OR "cross-sectional" OR crosssectional OR observation* OR longitudinal OR epidemiol*)
4. 1 AND 2 AND 3

Limitations: Studies involving human participants
Date of search: 23 November 2017
Result: 780 articles found

Embase

1. 'sleep disorder'/exp OR (('sleep'/exp OR sleep*:ab,ti,kw OR wake:ab,ti,kw OR awake:ab,ti,kw OR waking:ab,ti,kw OR awaking:ab,ti,kw OR somnolence*:ab,ti,kw OR somnolescent:ab,ti,kw OR REM:ab,ti,kw OR 'Circadian rhythm':ab,ti,kw) AND (disorder*:ab,ti,kw OR disturb*:ab,ti,kw OR paroxysmal:ab,ti,kw)) OR 'Sleep problem*':ab,ti,kw OR 'Sleep difficult*':ab,ti,kw OR 'Sleep Deprivation*':ab,ti,kw OR 'Sleep Fragmentation*':ab,ti,kw OR 'Insufficient Sleep syndrome*':ab,ti,kw OR 'Nyctohemeral Rhythm*':ab,ti,kw OR 'Sleep Phase Syndrome*':ab,ti,kw OR 'jet lag*':ab,ti,kw OR hypersomnolence*:ab,ti,kw OR 'hyper-somnolence*':ab,ti,kw OR hypersomnia*:ab,ti,kw OR 'hyper-somnia*':ab,ti,kw OR 'Kleine-Levin':ab,ti,kw OR narcoleps*:ab,ti,kw OR cataplex*:ab,ti,kw OR Gelineau*:ab,ti,kw OR 'nocturnal myoclonus syndrome*':ab,ti,kw OR (('Leg Movement*':ab,ti,kw OR 'Limb Movement*':ab,ti,kw) AND sleep*:ab,ti,kw) OR 'restless leg*':ab,ti,kw OR 'Willis Ekbom':ab,ti,kw OR 'Wittmaack Ekbom':ab,ti,kw OR 'sleep apnea*':ab,ti,kw OR 'nocturnal apnea*':ab,ti,kw OR 'sleep hypopnea*':ab,ti,kw OR 'sleep apnoea*':ab,ti,kw OR 'nocturnal apnoea*':ab,ti,kw OR 'sleep hypopnoea*':ab,ti,kw OR 'sleepdisordered breathing':ab,ti,kw OR insomnia*:ab,ti,kw OR parasomnia*:ab,ti,kw OR 'Nocturnal Dystonia*':ab,ti,kw OR 'Sleep paralys*':ab,ti,kw OR 'Night Terror*':ab,ti,kw OR 'Pavor Nocturnus':ab,ti,kw OR Somnambulis*:ab,ti,kw OR Sleepwalking:ab,ti,kw OR 'Sleep walking':ab,ti,kw OR 'Nocturnal Wandering*':ab,ti,kw OR 'Jactatio Capitis Nocturna':ab,ti,kw OR 'Nocturnal Leg Cramp*':ab,ti,kw OR 'Sleep talking':ab,ti,kw OR 'Sleep start*':ab,ti,kw OR ((periodic:ab,ti,kw OR repetitive:ab,ti,kw) AND movement*:ab,ti,kw AND sleep*:ab,ti,kw) OR plms:ab,ti,kw OR plmd:ab,ti,kw
2. 'neoplasm'/exp OR adenoma*:ab,ti,kw OR anticarcinogen*:ab,ti,kw OR blastoma*:ab,ti,kw OR cancer*:ab,ti,kw OR carcinogen*:ab,ti,kw OR carcinom*:ab,ti,kw OR carcinosarcoma*:ab,ti,kw OR chordoma*:ab,ti,kw OR germinoma*:ab,ti,kw OR gonadoblastoma*:ab,ti,kw OR hepatoblastoma*:ab,ti,kw OR 'hodgkin disease':ab,ti,kw OR 'hodgkin s disease':ab,ti,kw OR 'hodgkins disease':ab,ti,kw OR leukemi*:ab,ti,kw OR lymphangioma*:ab,ti,kw OR lymphangiomyoma*:ab,ti,kw OR lymphangiosarcoma*:ab,ti,kw OR lymphom*:ab,ti,kw OR malignan*:ab,ti,kw OR melanom*:ab,ti,kw OR meningioma*:ab,ti,kw OR esenchymoma*:ab,ti,kw OR mesonephroma*:ab,ti,kw OR metasta*:ab,ti,kw OR neoplas*:ab,ti,kw OR neuroma*:ab,ti,kw OR nsclc:ab,ti,kw OR oncogen*:ab,ti,kw OR oncolog*:ab,ti,kw OR paraneoplastic:ab,ti,kw OR plasmacytoma*:ab,ti,kw OR precancerous:ab,ti,kw OR sarcoma*:ab,ti,kw OR teratocarcinoma*:ab,ti,kw OR teratoma*:ab,ti,kw OR tumor*:ab,ti,kw OR tumour*:ab,ti,kw
3. 'cohort analysis'/exp OR 'cross-sectional study'/exp OR 'observational study'/exp OR 'prospective study'/exp OR 'longitudinal study'/exp OR prospectiv*:ab,ti,kw OR cohort*:ab,ti,kw OR prevalen*:ab,ti,kw OR incidenc*:ab,ti,kw OR 'crosssectional': ab,ti,kw OR crosssectional:ab,ti,kw OR observation*:ab,ti,kw OR longitudinal:ab,ti,kw OR epidemiol*:ab,ti,kw
4. 1 AND 2 AND 3

Limitations: Studies involving human participants, not conference publications
Date of search: 24 November 2017
Result: 5,416 articles found

Appendix 2. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	NA
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

Appendix 2 continued.

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Chapter III

Poor sleep quality among newly diagnosed head and neck cancer patients: prevalence and associated factors

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Supportive Care in Cancer (2021) 29: 1035–1045

Abstract

Background

Head and neck cancer (HNC) patients often suffer from distress attributed to their cancer diagnosis which may disturb their sleep. However, there is lack of research about poor sleep quality among newly diagnosed HNC patients. Therefore, our aim was to investigate the prevalence and the associated factors of poor sleep quality among HNC patients before starting treatment.

Materials and methods

A cross-sectional study was conducted using the baseline data from NET-QUBIC study, an ongoing multi-center cohort of HNC patients in the Netherlands. Poor sleep quality was defined as a Pittsburgh Sleep Quality Index (PSQI) total score of > 5. Risk factors examined were sociodemographic factors (age, sex, education level, living situation), clinical characteristics (HNC subsite, tumor stage, comorbidity, performance status), lifestyle factors, coping styles, and HNC symptoms.

Results

Among 560 HNC patients, 246 (44%) had poor sleep quality before start of treatment. Several factors were found to be significantly associated with poor sleep: younger age (odds ratio [OR] for each additional year 0.98, 95% CI 0.96 – 1.00), being female (OR 2.6, 95% CI 1.7 – 4.1), higher passive coping style (OR 1.18, 95% CI 1.09 – 1.28), more oral pain (OR 1.10, 95% CI 1.01 - 1.19), and less sexual interest and enjoyment (OR 1.13, 95% CI 1.06 – 1.20).

Conclusion

Poor sleep quality is highly prevalent among HNC patients before start of treatment. Early evaluation and tailored intervention to improve sleep quality are necessary to prepare these patients for HNC treatment and its consequences.

Introduction

More than 800,000 people worldwide were newly diagnosed with head and neck cancer (HNC) in 2018 [1]. There is a growing attention to maximize health-related quality of life (HRQoL) of newly diagnosed HNC patients [2]. These patients often suffer from emotional distress and concerns related to the future consequences of HNC itself and its treatment [3, 4], which may affect their sleep quality. Sleep quality before the start of cancer treatment is also known to be associated with HRQoL throughout the cancer trajectory [5, 6], thus early detection of poor sleep quality is necessary to initiate prehabilitation strategy to optimize HRQoL during and after HNC treatment [7].

Nonetheless, little is known about sleep quality among newly diagnosed HNC patients. A recent systematic review found a wide prevalence range of 16 to 66% for various definitions of sleep disturbances among HNC patients before treatment [8]. Additionally, most of the included studies did not use validated instrument to measure sleep quality as reported by the patients themselves [8]. To illustrate, only two studies among newly diagnosed HNC patients used the Pittsburgh sleep quality index (PSQI) [9, 10], a validated and most widely used self-report instrument for sleep quality in clinical and non-clinical populations [11]. Using a PSQI total score cut-off of > 5, these two studies found that 37% of their patients had poor sleep quality [9, 10]. Since these studies only included nasopharyngeal cancer patients [9, 10], the prevalence of poor sleep quality among a more generalizable sample of newly diagnosed HNC patients is yet to be examined.

Furthermore, more insight is needed on the factors associated with poor sleep quality among HNC patients before treatment. Only two studies have examined this question thus far and found that age, marital status, HNC subsite, smoking status, and physical activity were significantly associated factors [12, 13], implying the importance to assess these factors in sleep quality evaluation among newly diagnosed HNC patients. Neither of these studies, however, examined two important factors among newly diagnosed HNC patients: coping styles and HNC symptoms. Coping styles determine how someone perceives stressful life events, such as being diagnosed with cancer. Although the effectiveness of coping style may depend on the context of the stressor, certain coping styles such as avoidance coping, substance use, and behavioral and mental disengagement are found to be associated with more psychological distress among HNC patients before starting treatment [14]. Avoidance coping style in particular is found to be associated with poor sleep among cancer patients in general [15, 16]. So far, there is no research on whether specific coping styles are associated with poor sleep quality among newly diagnosed HNC patients. Furthermore, patients recently diagnosed with HNC often suffer from oral pain and swallowing problems [17] which may disrupt their sleep quality.

Insight into poor sleep quality among newly diagnosed HNC patients may help healthcare providers to design a better sleep intervention for those who already need it before starting treatment. Therefore, we aimed to examine the prevalence of poor sleep quality among HNC patients before start of treatment, and to examine the association of poor sleep quality with sociodemographic factors, clinical characteristics, lifestyle factors, coping style, and HNC-specific symptoms.

Patients and methods

Study population

Data of the prospective NETherlands QUality of Life and BIomedical Cohort study in head and neck cancer (NET-QUBIC) [18] was used. In the NET-QUBIC study, 739 newly diagnosed HNC patients from HNC centers in 5 university medical centers and 2 of their satellite hospitals in the Netherlands were included between March 2014 and June 2018. Inclusion criteria were: being diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or neck lymph node metastasis of an unknown primary tumor; being 18 years or older; having curative treatment intention; and being able to write, read, and speak Dutch. Exclusion criteria were having severe psychiatric comorbidity (e.g., schizophrenia, Korsakoff's syndrome, severe dementia), lymphoma, thyroid cancer, nasopharyngeal cancer, malignancy of skin, or malignancy of salivary glands. The NET-QUBIC study was approved by the Medical Ethical Committee of the coordinating center (Amsterdam UMC, location VUmc, document number: 2013.301[A2018.307]-NL45051.029.13). Detailed procedure of the NET-QUBIC study can be found elsewhere [18].

Measures

The ongoing NET-QUBIC study encompasses measurements at baseline and at 3-, 6-, 12-, 24-, 36-, 48-, and 60-month follow-up. In the present study, we used the baseline data, which were collected shortly after the diagnosis and before cancer treatment was started.

Sleep quality was measured using the PSQI, which was filled-in by the patients themselves [19]. Its validity and reliability have been confirmed both in general population [20] and in cancer patients [21, 22]. PSQI consists of 19 items across seven components of sleep quality and disturbances: (1) subjective sleep quality (i.e., one item 'How would you rate your sleep quality overall?'), (2) sleep onset latency (i.e., two items asking time needed to fall asleep and its frequency in a week; poor sleep onset is defined as needing ≥ 30 minutes to fall asleep [23]), (3) sleep duration (i.e., one item 'How many hours of actual sleep do you get at night?'; ≤6 hours is associated with worse survival

among cancer patients [24]), (4) sleep efficiency (i.e., a percentage calculated by dividing time asleep by time spent in bed and multiplied by 100; <85% indicates poor efficiency [23]), (5) sleep disturbances (i.e., ten items about specific reasons for the sleep disturbances and their frequency), (6) use of sleep medication (i.e., one item 'How often have you taken medicine to help you sleep?'), and (7) daytime dysfunction (i.e., two items asking the frequency of staying awake during daytime activity and the extent of difficulty to maintain enthusiasm to get things done) [19]. A total score (also called global score) is calculated by first scaling each component score into a 0 to 3 score then summing all component scores, resulting in a score ranging from 0 to 21; higher scores indicate worse sleep quality. Our main outcome, poor sleep quality, is defined by a total PSQI score of > 5 [19, 20]. In addition, we examined questions in the PSQI (not included in the total score calculation) which assessed the frequency of the respondent's bed partner/roommate noticing certain behaviors during the respondent's sleep. This information is clinically relevant as an indication of specific sleep disorders such as sleep apnea [25].

We examined the following sociodemographic factors: sex and age (from medical records), living situation (living together / alone, from interview), education level (low / middle / high according to the standard classification of education level in the Netherlands [26], from interview), and having a bed partner (yes / no, from the PSQI). The interview was conducted by trained field workers during house-visit measurements. This interview also included other outcomes which were out of the scope of the present study [18]. Clinical characteristics (i.e., HNC subsite and stage, comorbidity, and performance status) were retrieved from medical records. Comorbidity was scored using the adult comorbidity evaluation (ACE-27). The ACE-27 measures the number and severity of 27 medical conditions, and is summarized into four categories: no comorbidity, mild comorbidity, moderate comorbidity, or severe comorbidity [27]. The ACE-27 has been validated among HNC patients [28]. The patients' performance status (i.e., the patient's level of functioning seen from their daily activity, physical ability, and self-care) was measured using the one-item Eastern cooperative oncology group (ECOG) score, which ranges from 0 (fully active) to 4 (completely disabled) [29].

Coping styles were measured by the self-reported 47-item Utrecht coping list (UCL) [30]. Each item ranges from 0 (never or seldom) to 3 (very often). The UCL measures active coping (i.e., evaluating the situation from all perspectives and taking action to solve the problem; 7 items), palliative reaction (i.e., finding distractions against the problem and seeking for manners to feel better; 8 items), avoidance coping (i.e., avoiding the situation and letting it to be solved by itself; 8 items), seeking social support (i.e., seeking help and understanding from the others, expressing worries; 6 items), passive coping (i.e., taking the blame for the situation, worrying about things in the past, withdrawing into oneself; 7 items), expression of emotions (i.e., expressing anger or

abreaction; 3 items), and comforting thoughts (i.e., assuring one's self that things will get better, that things could have been worse, or that the others' may also have similar difficulties; 5 items) [30, 31]. For each coping style, a sum score was calculated, where a higher score indicates higher extent the specific coping style.

HNC symptoms were self-reported using the European organization for research and treatment of cancer quality of life questionnaire - HNC-specific module (EORTC QLQ-H&N35) [32]. All symptom scales were included: oral pain (4 items), swallowing problems (4 items), sense problems (2 items), speech problems (3 items), trouble with social eating (4 items), trouble with social contact (5 items), and less sexual interest and enjoyment (2 items). Also, we included Likert-scale single items measuring teeth problems, problems with opening mouth, dry mouth, sticky saliva, coughing, and feeling ill, as well as dichotomous single items measuring use of painkillers, use of nutritional supplements, use of feeding tube, weight loss and weight gain. Each symptom scale and Likert-scale single item was converted into a score ranging from 0 to 100, according to the EORTC guidelines. A higher score indicates a higher level of symptoms or problems.

The following lifestyle factors were examined: physical activity, body mass index (BMI), smoking status and alcohol intake. Physical activity was assessed using the 13-item physical activity scale for the elderly (PASE) with total score ranging from 0 to 400; a higher score indicates higher physical activity [33]. The validity and reliability of this patient-reported outcome measure has been previously confirmed among cancer patients [34]. BMI was measured by a trained field worker using a standardized procedure during house visit. Smoking status (not smoking/smoking every day at the time of assessment) and excessive alcohol consumption (>14 units of alcohol per week for women or >21 units of alcohol per week for men [35]) were self-reported using study-specific items .

Statistical analysis

Only participants who completed the main outcome measure (PSQI) were included in the analysis. Sociodemographic and clinical characteristics of participants who were included versus excluded from the analysis were compared using t-test (for continuous variables) or chi-square test (for categorical variables). For the included patients, we performed descriptive analyses: mean scores with standard deviation (SD) or medians with interquartile range (IQR) for continuous variables, frequencies with proportions for categorical variables. We also examined the proportions and mean scores (with SD) or median (with IQR) of the PSQI total and component scores.

To examine the differences among patients with good and poor sleep, first, their sociodemographic, clinical, and lifestyle characteristics, as well as coping styles and HNC symptoms were compared using chi-square (categorical variables) and t-tests or

Mann-Whitney tests (continuous variables). Then, forward multivariable logistic regression analyses were performed on each category of associated factors separately (i.e., sociodemographic, coping style, clinical factors, HNC symptoms, and lifestyle factors) using a *p*-value for entry of < 0.05. Subsequently, we performed logistic regression analyses using a forward selection of all significant variables across all categories, resulting in the final model. In all regression models, HNC symptom and item scores which ranged from 0 to 100 were rescaled into 10-point increments. All statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp. 2017).

Results

Study population

Among the 739 eligible patients, 179 (24%) did not have available PSQI scores and were excluded from our analyses. Age, gender, education level, HNC subsite, and HNC stage were similar between patients with (n=560, 76%) and without PSQI data. However, patients providing PSQI data more often lived with others, had better ECOG performance status, and less comorbidity compared to the patients not providing PSQI data (Table 1). There were 171 (21%) missing values on BMI, therefore this variable was not included in the analysis. For all other variables missing values ranged from 7 (1.3%) to 43 (7.7%). Since only 5 patients (0.9%) used a feeding tube, we did not include this variable in the analysis.

Our final sample of patients with PSQI data were mostly men (75%), on average 63 years old (SD=9), and low educated (42%). Most patients (79%) lived with others (i.e., with a partner, child, and/or housemate) and 70% had a bed partner. About one third (32%) had no comorbidity (Table 3).

Sleep quality

The median PSQI total score was 5 (IQR = 3 - 8). There were 246 HNC patients who were classified as having poor sleep (PSQI > 5; 44%). The median time needed to fall asleep (i.e., sleep latency) was 13 minutes (IQR=8 – 30) and the mean sleep duration was 7 hours (SD=1). Among all patients, 13% slept ≤ 6 hours in a night, 42% had <85% sleep efficiency, 16% could not fall asleep within 30 minutes at least three nights a week, and 45% reported nighttime or early morning awakening at least three times a week. At least once in a week, 15% of the patients used medication to improve their sleep and 5% experienced difficulties staying awake during the day. Questions answered by 417 bed partners or roommates revealed that 173 (43%) patients snored loudly and 13% of the patients had long breathing pause at least once a week. Mean

(SD) or median (IQR), as well as the proportions of each component score are presented in Table 2.

Table 1. Characteristics of patients with available versus unavailable PSQI data

	Available PSQI data (n=560)	**Unavailable PSQI data (n=179)**	***p*-value**
Age (mean, SD)	63 (9)	63 (11)	0.33
Women	142 (25%)	48 (27%)	0.70
Education level[a,b]			
Low	215 (42%)	64 (49%)	0.19
Middle	136 (26%)	35 (27%)	
High	166 (32%)	32 (24%)	
Living alone[a]	**108 (21%)**	**56 (43%)**	**<0.001**
HNC location			
Oral cavity	157 (28%)	42 (24%)	0.34
Oropharynx[c]	198 (35%)	64 (36%)	
Hypopharynx	35 (6%)	17 (10%)	
Larynx	152 (27%)	53 (30%)	
Unknown primary	18 (3%)	3 (2%)	
HNC stage			
I	134 (24%)	29 (16%)	0.086
II	103 (18%)	29 (16%)	
III	90 (16%)	37 (21%)	
IV	233 (42%)	84 (47%)	
ECOG performance status			
0	**398 (71%)**	**109 (61%)**	**0.012**
1 or more	**162 (29%)**	**70 (39%)**	
Comorbidity[a]			
None	**172 (32%)**	**32 (19%)**	**0.002**
Mild	**203 (38%)**	**61 (37%)**	
Moderate	**109 (20%)**	**46 (28%)**	
Severe	**50 (9%)**	**26 (16%)**	

[a] There were 91 missing values on education level, 90 missing values on living arrangement, and 40 missing values on comorbidity.

[b] Low education level includes primary education, lower or preparatory vocational education, and intermediary general secondary education. Middle education level includes senior general secondary education and higher general secondary education. High education level includes higher professional education and university.

[c] Human papilloma virus (HPV) status of oropharynx cancer patients with available PSQI data was positive among 104 patients, negative among 67 patients, and not tested among 27 patients. For patients with unavailable PSQI data the HPV status was positive among 26 patients, negative among 32 patients, and not tested among 6 patients.

Table 2. Overview of PSQI components

PSQI component		Mean (SD) or median(IQR)	n (%)
Subjective sleep quality[a]		NA	
Component score	0 (very good)		137 (25)
	1 (fairly good)		303 (54)
	2 (fairly bad)		107 (19)
	3 (very bad)		12 (2)
Sleep latency, in minutes[b]		13 (8 - 30)	
Component score*	0		208 (39)
	1		196 (36)
	2		87 (16)
	3		47 (9)
Sleep duration, in hours[c]		7.1 (1.3)	
Component score	0 (>7 hours)		365 (65)
	1 (6-7 hours)		122 (22)
	2 (5-6 hours)		44 (8)
	3 (<5 hours)		26 (5)
Sleep efficiency[d]		NA	
Component score*	0 (>85%)		322 (58)
	1 (75-84%)		125 (23)
	2 (65-74%)		42 (7)
	3 (<65%)		64 (12)
Sleep disturbances[e]		NA	
Component score*	0		23 (4)
	1		328 (59)
	2		185 (33)
	3		22 (4)
Use of sleep medication[a]		NA	
Component score	0 (not during the past month)		460 (82)
	1 (<1/week)		15 (3)
	2 (1-2/week)		28 (5)
	3 (≥3/week)		56 (10)
Daytime dysfunction[a]		NA	
Component score*	0		250 (45)
	1		256 (46)
	2		50 (9)
	3		3 (0.5)

Table 2 continued.

PSQI component		Mean (SD) or median(IQR)	n (%)
Questions answered by bedpartner / roommate about patients' sleep behavior (n=417) [f]		NA	
	Loud snoring ≥1/week		173 (43)
	Long breathing pause ≥1/week		50 (12)
	Legs twitching ≥1/week		35 (9)
	Episodes of disorientation ≥1/week		4 (1)

* Component score is calculated from ≥ 2 items and rescaled to 0 to 3. Higher component score denotes worse complaints.

[a] Subjective sleep quality, use of sleep medication, and day dysfunction due to sleepiness could not be calculated for 1 patient.

[b] Sleep latency could not be calculated for 22 patients.

[c] Sleep duration could not be calculated for 3 patients.

[d] Sleep efficiency could not be calculated for 7 patients.

[e] Sleep disturbances could not be calculated for 2 patients.

[f] Missing from 11 patients on snoring, 16 on breathing pauses, 14 on legs twitching, and 12 on episodes of disorientation

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; NA, not applicable; SD, standard deviation

Factors associated with poor sleep quality

Univariate analyses revealed that patients with poor sleep (n=246) were more often women, younger, diagnosed with cancer in the oral cavity, using painkillers, or using nutritional supplements (Table 3). Furthermore, compared to good sleepers, poor sleepers used less active coping and more palliative reaction, passive coping, and expression of emotions. Also, poor sleepers had worse scores of all HNC symptoms except for speech problems, problems with opening mouth, coughing, and weight changes.

Multivariate logistic regression models on the separate domains of risk factors showed that poor sleep was significantly associated with sociodemographic factors (younger age, being female), coping style (more passive coping), clinical characteristics (HNC subsite, especially cancer in the oral cavity and oropharynx compared to larynx), and HNC symptoms (oral pain, less sexual interest and enjoyment, and feeling ill). Combining all of these significant variables in a logistic regression model, we found that younger age (odds ratio [OR] per increasing year of age = 0.98, 95% CI = 0.96 − 1.00, *p*-value = 0.049), being female (OR = 2.6, 95% CI = 1.7 − 4.1, *p*-value <0.001), higher passive coping style (OR = 1.18, 95% CI = 1.09 − 1.28, *p*-value <0.001), more oral pain (OR = 1.10, 95% CI = 1.01 − 1.19, *p*-value=0.023), and less sexual interest and enjoyment (OR = 1.13, 95% CI 1.06 − 1.20, *p*-value <0.001) corresponded to greater odds of having poor sleep (Table 4).

Table 3. Characteristics and group comparisons of patients with good sleep versus patients with poor sleep.

	All patients (n=560)	Good sleep (n=314)	Poor sleep (n=246)	p-value
Age (mean, SD)	63 (9)	**64 (9)**	**62 (9)**	**0.020**
Women, n (%)	142 (25)	**51 (36)**	**91 (64)**	**0.001**
Education, n (%)[a, b]				
Low	215 (42)	117 (54)	98 (46)	0.40
Middle	136 (26)	84 (62)	52 (38)	
High	166 (32)	95 (57)	71 (43)	
Living alone, n (%)[a]	108 (21)	59 (55)	49 (45)	0.59
Had bed partner, n (%)[a]	385 (70)	223 (58)	162 (42)	0.16
Coping, mean (SD) or median (IQR)[a]				
Active coping	11.7 (4)	**12 (4)**	**11.3 (4)**	**0.035**
Palliative reaction	9.3 (3)	**9 (4)**	**9.8 (4)**	**0.006**
Avoidance coping	7.3 (4)	7 (3)	7.5 (3)	0.068
Seeking social support	6.9 (3)	6.8 (3)	7.1 (3)	0.27
Passive coping	3 (1 - 5)	**2 (1 - 4)**	**3 (2 - 6)**	**<0.001**
Expression of emotions	2 (1 - 3)	**1 (0 - 3)**	**2 (1 - 3)**	**0.001**
Comforting thoughts	7.3 (2)	7.1 (2)	7.5 (3)	0.078
HNC location, n (%)				
Oral cavity	157 (28)	**74 (47)**	**83 (53)**	**0.008**
Oropharynx	198 (35)	**108 (55)**	**90 (45)**	
Hypopharynx	35 (6)	**19 (54)**	**16 (46)**	
Larynx	152 (27)	**103 (68)**	**49 (32)**	
Unknown primary	18 (3)	**10 (56)**	**8 (44)**	
HNC stage, n (%)				
I	134 (24)	84 (63)	50 (37)	0.24
II	103 (18)	59 (57)	44 (43)	
III	90 (16)	45 (50)	45 (50)	
IV	233 (42)	126 (54)	107 (46)	
ECOG performance status, n (%)				
0	398 (71)	231 (58)	167 (42)	0.16
1 or more	162 (29)	83 (51)	79 (49)	
Comorbidity, n (%)[a]				
None	172 (32)	102 (59)	70 (41)	0.42
Mild	203 (38)	113 (56)	90 (44)	
Moderate	109 (20)	62 (57)	47 (43)	
Severe	50 (9)	23 (46)	27 (54)	

Table 3 continued.

	All patients (n=560)	Good sleep (n=314)	Poor sleep (n=246)	p-value
Head-neck symptoms, mean (SD) or n (%)[a]				
Oral pain	26 (24)	**22 (22)**	**32 (26)**	**<0.001**
Swallowing problems	16 (21)	**13 (20)**	**19 (22)**	**<0.001**
Sense problems	8 (17)	**7 (14)**	**10 (19)**	**0.008**
Speech problems	19 (23)	17 (22)	20 (24)	0.16
Problems with social eating	11 (17)	**8 (15)**	**15 (19)**	**<0.001**
Problems with social contact	4 (10)	**3 (7)**	**6 (12)**	**<0.001**
Less sexual interest and enjoyment	26 (31)	**20 (27)**	**34 (34)**	**<0.001**
Teeth problems	16 (27)	**13 (25)**	**19 (30)**	**0.013**
Problems with opening mouth	12 (25)	10 (22)	14 (28)	0.053
Dry mouth	16 (23)	**13 (21)**	**19 (25)**	**0.001**
Sticky saliva	14 (24)	**12 (22)**	**17 (25)**	**0.017**
Coughing	23 (24)	22 (22)	25 (26)	0.11
Feeling ill	13 (23)	**9 (18)**	**18 (24)**	**<0.001**
Used painkillers[c]	299 (54%)	**141 (47%)**	**158 (53%)**	**<0.001**
Used nutritional supplements[c]	86 (16%)	**36 (42%)**	**50 (58%)**	**0.006**
Had weight loss[c]	133 (24%)	65 (49%)	68 (51%)	0.056
Had weight gain[c]	57 (10%)	29 (51%)	28 (49%)	0.40
Smoking daily, n (%)[a]	123 (22)	62 (50)	61 (50)	0.18
Excessive alcohol consumption, n (%)[a]	124 (22)	73 (59)	51 (41)	0.54
PASE global score, median (IQR)[a]	84 (43 - 144)	83 (46 - 134)	90 (39 - 154)	0.51

[a] Variables with missing values: 43 missing values on education, 42 on living arrangements, 7 on having bed partner, 4 – 10 on each UCL domain scores, 26 on comorbidity, 7 on all EORTC-H&N35 domains (except less sexual interest and enjoyment [missing=43], teeth problems [missing=12], problems with opening mouth [missing=9], sticky saliva [missing=8], coughing [missing=8], using painkillers [missing=10], using feeding tube [missing=8], had weight loss [missing=11], and had weight gain [missing=14]), 9 on smoking status, 7 on alcohol consumption, 7 on PASE score, 11 on snoring, and 16 on breathing pauses.

[b] Low education level includes primary education, lower or preparatory vocational education, and intermediary general secondary education. Middle education level includes senior general secondary education and higher general secondary education. High education level includes higher professional education and university.

[c] Item with yes/no answer response; the proportions of 'yes' were reported in the table

Abbreviations: HNC, Head and neck cancer; PASE, Physical activity scale for the elderly; SD, standard deviation; UCL, Utrecht Coping List.

Table 4. Final model of the multivariable logistic regression analyses with poor sleep (PSQI total score > 5) as outcome (n=516).

Covariates[a]	OR	p-value	95%CI
Age	0.98	0.049	0.96 – 1.00
Female	2.6	<0.001	1.7 – 4.1
Passive coping	1.18	<0.001	1.09 – 1.28
Oral pain[b]	1.10	0.023	1.01 – 1.19
Less sexual interest and enjoyment[b]	1.13	<0.001	1.06 – 1.20

[a] Covariates retained in the final model is based on forward selection of all significant variables of each category, with entry criteria *p*-value of <0.05. Nagelkerke's R=0.21.
[b] Oral pain and less sexual interest and enjoyment scores were transformed into 10-point increments.
Abbreviations: CI, confidence interval; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index

Discussion

In this study, we examined the prevalence of poor sleep quality among HNC patients before start of treatment and investigated the associated factors. Almost half of the patients in this study were categorized as poor sleepers. This prevalence is higher than prevalence in the general population (36%) [20], thus emphasizing the importance to incorporate sleep evaluation shortly after HNC diagnosis. Regarding the PSQI component scores, we found that a high proportion of patients reported poor sleep efficiency, difficulty to fall asleep, and nighttime or early morning awakenings; these three complaints are particularly relevant as they are the most commonly reported symptoms of insomnia [23]. Comparing our prevalence rates with those of similar studies was not possible because no other study has been published using both a similar population of HNC patients and a validated self-reported measure for sleep quality.

We found that younger age, being female, having passive coping style, more oral pain, and less sexual interest and enjoyment were the most significant factors associated with poor sleep. In the general population, older adults tend to experience age-related changes in sleep-wake architecture, such as more sleep awakenings, less deep sleep, and less sleep efficiency [23]. This is apparently not the case for HNC patients, as we found that it was younger patients who had worse sleep quality. This is in line with findings from two previous studies among HNC patients before treatment [12, 13]. These findings may be attributed to fear of cancer progression which is higher among younger HNC patients before treatment [36]. Patients who are diagnosed with cancer at a younger age also experience higher psychological distress compared to their older counterparts [37], which may contribute to their higher risk of having poor sleep.

The greater odds of having poor sleep among women in our study is consistent with findings among general population in the Netherlands [38]. Differences in the physiology

of sex hormones as well as circadian rhythms among men and women may explain the differences of sleep quality between the sexes [39]. However, previous studies examining poor sleep among pre-treated HNC patients reported different findings. The cause of this disagreement is unclear, although it may be in part due to the differences in defining sleep quality and the associated factors examined in the study. Using a single item ('How much is a problem is sleeping for you?'), Zhou and colleagues compared sex proportions of patients with severe sleep problem (n=45) with those who had no, mild, or moderate problems (n=281); they found that slightly more females had severe sleep problems, although this was not statistically significant [13]. These findings suggest that a dichotomized Likert-scale item is not informative enough to illustrate sex differences in poor sleep quality. On the other hand, Duffy and colleagues, who also looked at depressive symptoms in relation to sleep quality, found that depressive symptoms, and not sex, are associated with sleep quality [12]. Whether sex differences on sleep quality are completely attributed to depressive symptoms remains questionable, since depressive symptoms among both men and women seem to affect sleep quality in different ways [40, 41]. More research is needed to assess the complex relationship of depressive symptoms and sleep quality among men and women with HNC.

We found a significant association between poor sleep and passive coping style. Diagnosis of cancer, as a form of distress, may be perceived differently among HNC patients and its effect on sleep quality may be determined by coping style. No specific coping style is inherently positive or negative since certain coping styles can be effective respective of the onset and context of the distress [42]. However, coping strategies such as avoidance, denial, substance use, abreaction, and behavioral and mental disengagement are known to be related to psychological distress among newly-diagnosed HNC patients [14, 43]. We found that sleep quality before HNC treatment is associated with passive coping style, which comprises worrying about things in the past, withdrawing into oneself, and taking the blame for the situation. Passive coping style is also found to be associated with psychological distress after HNC treatment [44]. Although our cross-sectional study may not be able to explain any causal relationship, a longitudinal research among general population found that substance use, behavioral disengagement, and distracting oneself, compared to other coping styles, are associated with higher risk of having insomnia after stress exposure [45]. Whether this is also the case for HNC patients after treatment starts remains to be examined in future research.

As expected, based on clinical practice, we found significant associations between poor sleep and HNC symptoms, more specifically oral pain and less sexual enjoyment. The relationship between pain, sexual problems, and sleep problems may be bidirectional. First of all, pain may disrupt sleep, while poor sleep may also lower one's pain threshold, thus increasing the perception of pain [46]. Sexual satisfaction may improve sleep quality through the release of oxytocin and prolactin levels, both of which are

neuropeptides involved in sleep regulation [47]. Lack of sleep, on the other hand, may result in fatigue and reduce sexual desire [48]. More research is needed to confirm whether sleep intervention before treatment can optimize symptom management in HNC patients throughout the cancer trajectory.

Strength and limitations

The strength of this study was that we used a large sample of 560 HNC patients from multiple hospitals in the Netherlands to investigate the association between sleep problems and various sociodemographic, clinical, and lifestyle factors as well as coping style and HNC symptoms. Moreover, our study was the first study so far to report on the prevalence of different components of sleep quality (as measured by the PSQI) among HNC patients before starting treatment. However, we found differences between patients who were included because their PSQI data were available (n=560) compared to those that did not (n=179); our study population consists of HNC patients with better performance status and less severe comorbidity. Our study may, therefore, underestimate the real prevalence of poor sleep quality among newly diagnosed HNC patients. In addition, the NET-QUBIC participants were not completely representative for the overall HNC population in the Netherlands [18], which may limit generalizability of our study findings to all HNC patients.

Conclusions

Poor sleep quality is highly prevalent among newly-diagnosed HNC patients and is associated with younger age, being female, passive coping style, more oral pain, and less sexuality interest and enjoyment. Our findings underline the need for early sleep evaluation among HNC patients already before starting treatment, as well as taking coping styles and HNC symptoms into consideration when implementing sleep intervention.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394-424.
2. Smith JD, Shuman AG, Riba MB. Psychosocial issues in patients with head and neck cancer: an updated review with a focus on clinical interventions. Current psychiatry reports. 2017;19(9):56.
3. Fingeret MC, Vidrine DJ, Reece GP, Gillenwater AM, Gritz ER. Multidimensional analysis of body image concerns among newly diagnosed patients with oral cavity cancer. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2010;32(3):301-9.
4. Posluszny DM, Dougall AL, Johnson JT, Argiris A, Ferris RL, Baum A, et al. Posttraumatic stress disorder symptoms in newly diagnosed patients with head and neck cancer and their partners. Head & neck. 2015;37(9):1282-9.
5. Clevenger L, Schrepf A, Degeest K, Bender D, Goodheart M, Ahmed A, et al. Sleep disturbance, distress, and quality of life in ovarian cancer patients during the first year after diagnosis. Cancer. 2013;119(17):3234-41.
6. Dean GE, Sabbah EA, Yingrengreung S, Ziegler P, Chen H, Steinbrenner LM, et al. Sleeping with the enemy: sleep and quality of life in patients with lung cancer. Cancer nursing. 2015;38(1):60-70.
7. Chen D, Yin Z, Fang B. Measurements and status of sleep quality in patients with cancers. Supportive Care in Cancer. 2018;26(2):405-14.
8. Santoso AM, Jansen F, de Vries R, Leemans CR, van Straten A, Verdonck-de Leeuw IM. Prevalence of sleep disturbances among head and neck cancer patients: a systematic review and meta-analysis. Sleep medicine reviews. 2019.
9. Mo YL, Li L, Qin L, Zhu XD, Qu S, Liang X, et al. Cognitive function, mood, and sleep quality in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer: a prospective study. Psycho-Oncology. 2014;23(10):1185-91.
10. Qin L, Mo Y-L, Li L, Wei Z-J, Zhu X-D, Yin X, et al. Sleep characteristics and psychological symptoms in patients with locally advanced nasopharyngeal carcinoma before and after intensity-modulated radiotherapy and concurrent chemotherapy. Psychology, health & medicine. 2015;20(6):662-9.
11. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. Sleep Medicine Reviews. 2016;25:52-73.
12. Duffy SA, Khan MJ, Ronis DL, Fowler KE, Gruber SB, Wolf GT, et al. Health behaviors of head and neck cancer patients the first year after diagnosis. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2008;30(1):93-102.
13. Zhou ES, Clark K, Recklitis CJ, Obenchain R, Loscalzo M. Sleepless from the Get Go: Sleep Problems Prior to Initiating Cancer Treatment. International Journal of Behavioral Medicine. 2018;25(5):502-16.
14. Morris N, Moghaddam N, Tickle A, Biswas S. The relationship between coping style and psychological distress in people with head and neck cancer: A systematic review. Psycho-Oncology. 2018;27(3):734-47.
15. Hoyt MA, Thomas KS, Epstein DR, Dirksen SR. Coping style and sleep quality in men with cancer. Annals of Behavioral Medicine. 2009;37(1):88-93.
16. Thomas KS, Bower J, Hoyt MA, Sepah S. Disrupted sleep in breast and prostate cancer patients undergoing radiation therapy: the role of coping processes. Psychooncology. 2010;19(7):767-76.
17. Molassiotis A, Rogers M. Symptom experience and regaining normality in the first year following a diagnosis of head and neck cancer: a qualitative longitudinal study. Palliative & supportive care. 2012;10(3):197-204.
18. Verdonck-de Leeuw IM, Jansen F, Brakenhoff RH, Langendijk JA, Takes R, Terhaard CHJ, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal

prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. BMC Cancer. 2019;19(1):765.
19. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213.
20. Hinz A, Glaesmer H, Brähler E, Löffler M, Engel C, Enzenbach C, et al. Sleep quality in the general population: psychometric properties of the Pittsburgh Sleep Quality Index, derived from a German community sample of 9284 people. Sleep medicine. 2017;30:57-63.
21. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. Journal of pain and symptom management. 2004;27(2):140-8.
22. Tzeng JI, Fu Y-W, Lin C-C. Validity and reliability of the Taiwanese version of the Pittsburgh Sleep Quality Index in cancer patients. International Journal of Nursing Studies. 2012;49(1):102-8.
23. Morin CM, Espie CA. Clinical features of insomnia. Insomnia: A clinical guide to assessment and treatment
Springer Science & Business Media; 2007. p. 16.
24. Collins KP, Geller DA, Antoni M, Donnell DM, Tsung A, Marsh JW, et al. Sleep duration is associated with survival in advanced cancer patients. Sleep medicine. 2017;32:208-12.
25. Fedson AC, Pack AI, Gislason T. Frequently used sleep questionnaires in epidemiological and genetic research for obstructive sleep apnea: a review. Sleep medicine reviews. 2012;16(6):529-37.
26. (CBS) SN. Standaard Onderwijsindeling 2016 The Hague: CBS Statline; 2016 [Available from: https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/onderwijs-en-beroepen/standaard-onderwijsindeling--soi--/standaard-onderwijsindeling-2016.
27. Piccirillo J, Costas I, Claybour P, Borah A, Grove L, Jeffe D. The measurement of comorbidity by cancer registries. J Registry Manage. 2003;30(1):8-15.
28. Piccirillo JF. Importance of comorbidity in head and neck cancer. The Laryngoscope. 2000;110(4):593-602.
29. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-55.
30. Schreurs P, Van de Willige G, Brosschot J, Tellegen B, Graus G. De Utrechtse Coping Lijst (Utrecht Coping Questionnaire). Lisse: Swets and Zeitlinger; 1993.
31. Hoekstra-Weebers JE, Wijnberg-Williams BJ, Jaspers JP, Kamps WA, van de Wiel HB. Coping and its effect on psychological distress of parents of pediatric cancer patients: a longitudinal prospective study. Psycho-Oncology. 2012;21(8):903-11.
32. Bjordal K, Ahlner-Elmqvist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncologica. 1994;33(8):879-85.
33. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. Journal of clinical epidemiology. 1993;46(2):153-62.
34. Liu RD, Buffart LM, Kersten MJ, Spiering M, Brug J, van Mechelen W, et al. Psychometric properties of two physical activity questionnaires, the AQuAA and the PASE, in cancer patients. BMC medical research methodology. 2011;11(1):30.
35. (CBS) SN. Lifestyle and (preventive) health examination; personal characteristics The Hague: CBS Statline; 2019 [updated 6 November 2019. 19 March 2019:[Available from: https://opendata.cbs.nl/statline/#/CBS/en/dataset/83021ENG/table?ts=1580381653038.
36. Miroševič Š, Prins JB, Selič P, Zaletel Kragelj L, Klemenc Ketiš Z. Prevalence and factors associated with unmet needs in post-treatment cancer survivors: A systematic review. European Journal of Cancer Care. 2019;28(3):e13060.

37. Krok JL, Baker TA, McMillan SC. Age differences in the presence of pain and psychological distress in younger and older cancer patients. Journal of Hospice & Palliative Nursing. 2013;15(2):107-13.
38. Kerkhof GA. Epidemiology of sleep and sleep disorders in The Netherlands. Sleep medicine. 2017;30:229-39.
39. Mong JA, Cusmano DM. Sex differences in sleep: impact of biological sex and sex steroids. Philosophical Transactions of the Royal Society B: Biological Sciences. 2016;371(1688):20150110.
40. Khan AA, Gardner CO, Prescott CA, Kendler KS. Gender differences in the symptoms of major depression in opposite-sex dizygotic twin pairs. American Journal of Psychiatry. 2002;159(8):1427-9.
41. Montagni I, Qchiqach S, Pereira E, Tully PJ, Tzourio C. Sex-specific associations between sleep and mental health in university students: a large cross-sectional study. Journal of American College Health. 2018:1-8.
42. Lazarus RS. Coping theory and research: Past, present, and future. Fifty years of the research and theory of RS Lazarus: An analysis of historical and perennial issues. 1993:366-88.
43. Sherman AC, Simonton S, Adams DC, Vural E, Hanna E. Coping with head and neck cancer during different phases of treatment. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2000;22(8):787-93.
44. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, De Bree R, Leemans CR. Distress in spouses and patients after treatment for head and neck cancer. The Laryngoscope. 2007;117(2):238-41.
45. Pillai V, Roth T, Mullins HM, Drake CL. Moderators and Mediators of the Relationship Between Stress and Insomnia: Stressor Chronicity, Cognitive Intrusion, and Coping. Sleep. 2014;37(7):1199-208A.
46. Wei Y, Blanken TF, Van Someren EJW. Insomnia Really Hurts: Effect of a Bad Night's Sleep on Pain Increases With Insomnia Severity. Frontiers in Psychiatry. 2018;9(377).
47. Lastella M, O'Mullan C, Paterson JL, Reynolds AC. Sex and Sleep: Perceptions of Sex as a Sleep Promoting Behavior in the General Adult Population. Frontiers in Public Health. 2019;7(33).
48. Holloway V, Wylie K. Sex drive and sexual desire. Curr Opin Psychiatry. 2015;28(6):424-9.

Chapter IV

Sleep quality trajectories from head and neck cancer diagnosis to six months after treatment

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Abstract

Objectives

Patients with head and neck cancer (HNC) often report disturbances in their sleep quality, impairing their quality of life. This study aims to examine the trajectories of sleep quality from diagnosis up to 6-month after treatment, as well as the pre-treatment risk factors for poor sleep trajectories.

Materials and Methods

Sleep quality (Pittsburgh sleep quality index) was measured shortly after diagnosis (pre-treatment), and at 3 and 6 months after finishing treatment. Patients were categorized into 5 trajectory groups. We examined the association of sleep quality trajectories with sociodemographic and clinical characteristics, coping style, HNC symptoms, and psychological distress.

Results

Among 412 included patients, about a half either had a persistent good sleep (37.6%) or an improving (16.5%) trajectory. About a third had a persistent poor sleep (21.8%) or worsening (10.9%) sleep trajectory. The remaining patients (13.1%), alternated between good and poor sleep. Using persistent good sleep as a reference outcome, persistent poor sleepers were more likely to be woman (odds ratio [OR]=1.98, 95% confidence interval [CI] 1.01 to 3.90), use painkillers prior to treatment (OR=2.52, 95% CI 1.33 to 4.77), and have more pre-treatment anxiety symptoms (OR=1.26, 95% CI 1.15 to 1.38).

Conclusion

Unfavorable sleep quality trajectories are prevalent among HNC patients from pre-treatment to 6-month after treatment. A periodic sleep evaluation starting shortly after HNC diagnosis is necessary to identify persistent sleep problems, especially among high-risk group.

Introduction

Patients with head and neck cancer (HNC) often suffer from various types of sleep disturbances before, during, as well as after treatment [1]. Before starting treatment, more than forty percent of HNC patients experienced poor sleep quality [2]. Poor sleep is a disabling condition as it leads to deteriorations in quality of life of HNC patients [3]. Moreover, it is associated with poorer treatment outcomes and is associated with higher mortality in cancer patients in general [4]. However, information about the course of sleep quality among HNC patients is limited. Studies examining group averages over time reported either stable [5], improving [6], or worsening [7] trends. No study so far examined the individual sleep quality trajectories among HNC patients, which can either be: (1) persistently good, (2) good sleep before treatment which then worsens, (3) alternating good and poor sleep over time, (4) poor sleep before treatment which then improves, and (5) persistently poor.

Next to obtaining information on the proportions of different sleep trajectories, it is important to understand which patients are at high risk so that sleep evaluation and intervention can be tailored and targeted to those who need it the most. So far, only two prospective longitudinal studies examined determinants of sleep quality among newly-diagnosed HNC patients [5, 6]. These studies found that poor sleep quality within one year after diagnosis was associated with being female, younger, unmarried, as well as having more depressive symptoms before start of treatment [5, 6]. We do not know yet whether these characteristics are also associated with certain sleep trajectories, for example persistent poor sleep (which may indicate a chronic problem), or worsening and alternating sleep quality (which may indicate higher vulnerability to have poor sleep recurrence in the future).

The aim of this study was to examine the proportion of patients in five sleep quality trajectories from time of HNC diagnosis to three and six months after treatment. In addition, we aimed to examine possible risk factors for poor sleep trajectories, including sociodemographic factors (age, sex, education level), clinical characteristics (comorbidity, HNC stage, cancer subsite, treatment intent), pre-treatment symptoms (HNC symptoms, depression and anxiety), and coping styles.

Material and Methods

Participants and procedures

We used data from the NETherlands QUality of Life and Biomedical Cohort (NET-QUBIC), an ongoing prospective observational cohort study among 739 HNC patients from 5 university medical centers and 2 partner hospitals in the Netherlands [8]. Patients

were recruited between March 2014 and June 2018. Inclusion criteria were being 18 years or older; being diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, or lymph node metastasis of an unknown primary tumor; having curative treatment intention; and being able to write, read, and speak Dutch. Exclusion criteria were having severe psychiatric comorbidity (e.g., schizophrenia, Korsakoff's syndrome, severe dementia); thyroid cancer; nasopharyngeal cancer; malignancy of skin; or malignancy of salivary glands. All participating patients provided informed consent. The study was approved by the Medical Ethical Committee of the coordinating center Amsterdam UMC, location VUmc (2013.301(A2018.307)-NL45051.029.13). Detailed information about the NET-QUBIC study procedures can be found in our previous publication [8]. NET-QUBIC encompasses measurements at baseline (i.e., shortly after diagnosis and before start of treatment) and at 3, 6, 12, 24, 36, 48, and 60 months follow-up (i.e., after finishing cancer treatment). In the present study, we used the data collected at baseline, 3 months (M3), and 6 months follow-up (M6).

Measures

The primary outcome, sleep quality, was measured using the Pittsburgh sleep quality index (PSQI) [9]. Its validity and reliability have been confirmed in cancer patients [10, 11]. PSQI contains 19 items on seven components of sleep quality and disturbances, each ranges from 0 to 3: subjective sleep quality, sleep onset latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction [9]. The PSQI total score ranges from 0 to 21; a higher total score indicates worse sleep quality. Poor sleep quality is defined by a total PSQI score of > 5 [9, 12]. We categorized HNC patients based on all possible trajectories of sleep quality: (1) persistent good sleepers (i.e., PSQI ≤ 5 at all time-points), (2) patients who were good sleepers at baseline (i.e., PSQI ≤ 5), but who became poor sleepers (i.e., PSQI > 5) at M3 and M6 or at M6 only, (3) patients who alternated between poor and good sleep, (4) poor sleepers at baseline who became good sleepers at M3 and M6 or at M6 only, and (5) persistent poor sleepers (i.e., PSQI > 5 at all time-points).

Sociodemographic factors were obtained from electronic medical records (for sex and age) and interview during a house visit (for living situation and education level). Clinical characteristics (i.e., HNC subsite, stage, comorbidity, and performance status) were retrieved from electronic medical records. Comorbidity (none to mild vs moderate to severe comorbidity) was scored using the adult comorbidity evaluation (ACE-27), taking into account the presence and severity of 27 medical conditions [13]. Performance status (i.e., the patient's level of functioning based on their daily activity, physical ability, and self-care) was measured using the one-item Eastern cooperative oncology group (ECOG) score, which ranges from 0 (fully active) to 4 (completely disabled) [14].

HNC symptoms were self-reported using the European organization for research and treatment of cancer quality of life questionnaire - HNC-specific module (EORTC QLQ-H&N35) [15]. EORTC QLQ-H&N35 includes the following symptoms: oral pain (4 items), swallowing problems (4 items), sense problems (2 items), speech problems (3 items), trouble with social eating (4 items), trouble with social contact (5 items), less sexual interest and enjoyment (2 items), and single items measuring teeth problems, problems with opening mouth, dry mouth, sticky saliva, coughing, and feeling ill. These symptom scores range from 0 (best possible) to 100 (worst possible). In addition, EORTC QLQ-H&N35 also measured the use of painkillers, use of nutritional supplements, use of feeding tube, weight loss, and weight gain (each single dichotomous item).

Coping style was self-reported using the 47-item Utrecht coping list (UCL) questionnaire [16]. The UCL measures one's coping style against stressors in general and includes active coping (7 items), palliative reaction (8 items), avoidance coping (8 items), seeking social support (6 items), passive coping (7 items), expression of emotions (3 items), and comforting thoughts (5 items) [16]. Each item ranges from 0 (never or seldom) to 3 (very often). For each coping style, all item scores were summed; a higher score indicates higher extent of the specific coping style. Detailed explanation about each coping style measured in UCL is elaborated elsewhere [16, 17].

Distress was defined as symptoms of depression and / or anxiety. This was assessed using the 14-item hospital anxiety and depression scale (HADS) [18]. The anxiety (HADS-A) and depression (HADS-D) subscales of HADS consist each of 7 items, each ranging from 0 to 3. Sum of items in each subscale ranges from 0 to 21; a higher score indicates higher extent of depression or anxiety symptoms. The validity of HADS among cancer patients has been confirmed [19]. A score of > 7 for each subscale indicates an increased risk of having depressive or anxiety disorder among cancer patients [20].

Statistical analysis

Patients who completed PSQI at baseline, M3, and M6 were included in the analyses. We compared sociodemographic and clinical characteristics of those who were included in the analyses versus those who were not. Subsequently, sociodemographic factors (sex, age, education level, living situation) and baseline clinical characteristics (comorbidity, performance status, HNC subsite, HNC stage, and treatment intent) as well as coping styles, HNC symptoms, and symptoms of depression and anxiety were compared between all sleep quality trajectories using analysis of variance (ANOVA, for means of continuous variables), and Chi-square test (for proportions of categorical variables); variables with P value < 0.01 were tested for pairwise comparisons. Pairwise comparisons were corrected for multiple testing using the Bonferroni correction. Subsequently, variables with $P<0.05$ were included as independent variables in a multivariable multinomial logistic regression analysis with forward selection method

(P<0.05 as entry criteria). In this regression analysis, we set persistent good sleep as a reference outcome and each sleep quality trajectory as predicted outcome. Collinearity was tested by calculating variance inflation factor (VIF) of each variable included in the model. All statistical analyses were performed using the IBM SPSS version 26 (IBM Corp., Armonk, NY USA).

Results

Study population

Among all patients included in the NET-QUBIC study (n=739), 708 were still alive at M6. Of these 708 patients, 87 patients dropped out due to physical condition (n=20), psychological condition (n=20), logistic reasons (n=24), time limitation (n=3), referred to a non-participating medical center (n=3), no longer interested to participate in the study (n=8), and unknown reasons (n=9). Among the 621 patients who remained in the study, 209 had missing PSQI data at T0, M3, and/or M6. As a result, 412 patients (i.e., those who completed PSQI at all time-points) were included in the analyses. These included patients tended to have higher education level, live together with housemate or relative, have better performance status, and have less comorbidity than those who were not included (Table 1). The included patients were on average 64 years old (standard deviation [SD]=9) and were in majority men (74.5%), lived together (81.1%), and had no functional disability (76.5%). A full description of all sociodemographic and clinical characteristics at baseline is presented in Table 2.

Table 1 Baseline characteristics patients with complete PSQI score (included in the analysis) versus patients with missing PSQI score at any time-point (not included in the analysis).

	Included patients (n=412)	**Patients not-included (n=327)**	**P value[a]**
Age (mean, SD)	64 (9)	63 (10)	.08
Female	105 (25.5%)	85 (26.0%)	.93
Education level[b]			
Low	151 (38.6%)	128 (49.8%)	.01
Middle	106 (27.1%)	65 (25.3%)	
High	134 (34.3%)	64 (24.9%)	
Living alone[b]	74 (18.9%)	90 (35.0%)	<.001
HNC location			
Oral cavity	116 (28.2%)	83 (25.4%)	.14
Oropharynx	144 (35.0%)	118 (36.1%)	

Table 1 continued.

	Included patients (n=412)	Patients not-included (n=327)	P value[a]
Hypopharynx	23 (5.6%)	29 (8.9%)	
Larynx	113 (27.4%)	92 (28.1%)	
Unknown primary	16 (3.9%)	5 (1.5%)	
HNC stage			
I	100 (24.3%)	63 (19.3%)	.12
II	80 (19.4%)	52 (15.9%)	
III	64 (15.5%)	63 (19.3%)	
IV	168 (40.8%)	149 (45.6%)	
Performance status			
0 (best possible / fully active)	315 (76.5%)	192 (58.7%)	<.001
1 or more	97 (23.5%)	135 (41.3%)	
Comorbidity[b]			
None	141 (35.4%)	63 (20.9%)	<.001
Mild	160 (40.2%)	104 (34.6%)	
Moderate	67 (16.8%)	88 (29.2%)	
Severe	30 (7.5%)	46 (15.3%)	
Treatment intent[c]			
Single treatment	228 (55.3%)	166 (50.8%)	.24
Combination treatment	184 (44.7%)	161 (49.2%)	

[a] P values obtained from comparison statistics: Chi-square test for categorical variables and t-test for normally distributed continuous variables. Statistical significance was defined by P value < 0.05

[b] There were 91 missing values on education level, 90 on living arrangements, and 40 on comorbidity score.

[c] Single treatment consists of surgery only or radiotherapy only. Combination treatment consists of chemoradiotherapy, surgery with radiotherapy, surgery with chemoradiotherapy, and radiotherapy with hyperthermic therapy.

Abbreviations: HNC, head and neck cancer; PSQI, Pittsburgh sleep quality index; SD, standard deviation.

Table 2 Baseline characteristics among all patients and among patients in the different sleep quality trajectories.

Characteristic	All patients, n=412	Persistent good sleep, n=155 (37.6%)	Good sleep, worsening, n=45 (10.9%)	Alternating sleep quality, n=54 (13.1%)	Poor sleep, improving, n=68 (16.5%)	Persistent poor sleep, n=90 (21.8%)	p-value[a]
Mean age (SD)	64 (9)	65 (9)	64 (8)	65 (11)	61 (9)	63 (10)	.06
Sex							
Male	307 (74.5%)	128 (82.6%)*	38 (84.4%)	44 (81.5%)	46 (67.6%)	51 (56.7%)*	<.001
Female	105 (25.5%)	27 (17.4%)*	7 (15.6%)	10 (18.5%)	22 (32.4%)	39 (43.3%)*	
Education level[b]							
Low	151 (38.6%)	59 (39.1%)	19 (43.2%)	15 (28.8%)	25 (42.4%)	33 (38.8%)	.77
Medium	106 (27.1%)	42 (27.8%)	14 (31.8%)	15 (28.8%)	14 (23.7%)	21 (24.7%)	
High	134 (34.3%)	50 (33.1%)	11 (25.0%)	22 (42.3%)	20 (33.9%)	31 (36.5%)	
Living arrangements[b]							
Living together[c]	318 (81.1%)	127 (84.1%)	36 (81.8%)	37 (71.2%)	50 (83.3%)	68 (80.0%)	.34
Living alone	74 (18.9%)	24 (15.9%)	8 (18.2%)	15 (28.8%)	10 (16.7%)	17 (20.0%)	
Coping styles, mean (SD)[b]							
Active coping	11.8 (3.8)	12.1 (4)	12.4 (3)	12.1 (4)	11.7 (4)	10.9 (4)	.11
Palliative reaction	9.4 (3.6)	9.1 (4)	9.3 (3)	9.5 (3)	9.7 (4)	9.7 (4)	.66
Avoidance coping	7.1 (3.3)	7.0 (3)	6.8 (3)	7.3 (3)	7.3 (3)	7.0 (3)	.90
Seeking social support	6.9 (3.2)	6.6 (3)	7.2 (3)	7.4 (3)	7.3 (3)	6.9 (4)	.37
Passive coping	3.2 (2.6)	2.4 (2)*†	3.1 (2)	3.1 (3)	3.8 (3)*	4.1 (3)†	<.001
Expression of emotions	1.8 (1.4)	1.7 (1)	1.8 (1)	1.9 (1)	1.9 (1)	2.1 (1)	.15
Comforting thoughts	7.2 (2.5)	7.0 (2)	7.4 (2)	7.3 (2)	7.4 (3)	7.4 (3)	.61

Table 2 continued.

Characteristic	All patients, n=412	Persistent good sleep, n=155 (37.6%)	Good sleep, worsening, n=45 (10.9%)	Alternating sleep quality, n=54 (13.1%)	Poor sleep, improving, n=68 (16.5%)	Persistent poor sleep, n=90 (21.8%)	p-value[a]
Comorbidity[b]							
None to mild	301 (75.6%)	121 (80.7%)	33 (75.0%)	35 (66.0%)	49 (77.8%)	63 (71.6%)	.23
Moderate to severe	97 (24.4%)	29 (19.3%)	11 (25.0%)	18 (34.0%)	14 (22.2%)	25 (28.4%)	
Performance status[d]							
0 (best possible / fully active)	315 (76.5%)	123 (79.4%)	36 (80.0%)	40 (73.5%)	50 (73.5%)	66 (73.3%)	.73
1 or more	97 (23.5%)	32 (20.6%)	9 (20.0%)	14 (25.9%)	18 (26.5%)	24 (26.7%)	
HNC subsite							
Oral cavity	116 (28.2%)	42 (27.8%)	10 (23.3%)	12 (23.5%)	21 (31.8%)	31 (36.5%)	.48
Oropharynx[e]	144 (35.0%)	51 (33.8%)	15 (34.9%)	20 (39.2%)	27 (40.9%)	31 (36.5%)	
Hypopharynx / Larynx	136 (33.0%)	58 (38.4%)	18 (41.9%)	19 (37.3%)	18 (27.3%)	23 (27.1%)	
Unknown primary[f]	16 (3.9%)	NA	NA	NA	NA	NA	
HNC clinical stage							
I/II	180 (43.7%)	76 (49.0%)	17 (37.8%)	21 (38.9%)	24 (35.3%)	42 (46.7%)	.27
III/IV	232 (56.3%)	79 (51.0%)	28 (62.2%)	33 (61.1%)	44 (64.7%)	48 (53.3%)	
Treatment intent							
Single treatment	228 (55.3%)	89 (57.4%)	25 (55.6%)	31 (57.4%)	30 (44.1%)	53 (58.9%)	.37
Combination treatment	184 (44.7%)	66 (42.6%)	20 (44.4%)	23 (42.6%)	38 (55.9%)	37 (41.1%)	

Table 2 continued.

Characteristic	All patients, n=412	Persistent good sleep, n=155 (37.6%)	Good sleep, worsening, n=45 (10.9%)	Alternating sleep quality, n=54 (13.1%)	Poor sleep, improving, n=68 (16.5%)	Persistent poor sleep, n=90 (21.8%)	p-value[a]
Single treatment modality (n=228)							
Surgery (including CO2-laser)	94 (41.2%)	41 (46.1%)	11 (44.0%)	8 (25.8%)	11 (36.7%)	23 (43.4%)	.36
Radiotherapy	134 (58.8%)	48 (53.9%)	14 (56.0%)	23 (74.2%)	19 (63.3%)	30 (56.6%)	
Combination treatment modality (n=184)							
Chemoradiotherapy or other combination[g]	112 (60.9%)	45 (68.2%)	11 (55.0%)	11 (47.8%)	21 (55.3%)	24 (64.9%)	.38
Surgery and (chemo) radiotherapy	72 (39.1%)	21 (31.8%)	9 (45.0%)	12 (52.2%)	17 (44.7%)	13 (35.1%)	
HNC symptoms, mean (SD) or n (%)[b]							
Oral pain	24 (23)	21 (21)	26 (24)	18 (18)	29 (26)	27 (25)	.02
Swallowing problems	13 (19)	10 (18)	18 (21)	11 (19)	16 (19)	16 (20)	.046
Sense problems	7 (15)	6 (13)	8 (15)	8 (19)	10 (17)	6 (15)	.36
Speech problems	18 (11)	16 (23)	17 (18)	17 (24)	23 (27)	16 (19)	.29
Problems with social eating	10 (16)	6 (12)*	11 (19)	10 (19)	16 (19)*	11 (16)	.001

Table 2 continued.

Characteristic	All patients, n=412	Persistent good sleep, n=155 (37.6%)	Good sleep, worsening, n=45 (10.9%)	Alternating sleep quality, n=54 (13.1%)	Poor sleep, improving, n=68 (16.5%)	Persistent poor sleep, n=90 (21.8%)	p-value[a]
Problems with social contact	4 (9)	2 (7)	4 (8)	3 (8)	6 (13)	5 (10)	.08
Less sexual interest and enjoyment	26 (31)	18 (27)*	30 (25)	21 (31)	32 (33)	35 (34)*	<.001
Teeth problems	14 (26)	12 (24)	13 (26)	12 (25)	18 (31)	17 (27)	.30
Problems with opening mouth	11 (24)	11 (22)	10 (22)	5 (18)	14 (27)	13 (29)	.28
Dry mouth	15 (22)	11 (20)	13 (23)	15 (22)	17 (23)	18 (24)	.14
Sticky saliva	12 (22)	9 (20)	19 (26)	13 (22)	13 (23)	13 (20)	.09
Coughing	21 (24)	17 (22)	26 (25)	24 (25)	22 (25)	24 (26)	.10
Feeling ill	11 (21)	5 (14)*,†,‡	18 (23)*	11 (22)	16 (25) †	14 (22)‡	<.001
Used painkillers, n (%)	202 (49.8%)	56 (36.6%)*	26 (59.1%)	23 (44.2%)	35 (52.2%)	62 (68.9%)*	<.001
Used nutritional supplements, n (%)	51 (12.5%)	13 (8.4%)	6 (13.3%)	8 (15.4%)	11 (16.2%)	13 (14.4%)	.42
Used feeding tube[h] n (%)	2 (0.5%)	NA	NA	NA	NA	NA	NA
Had weight loss, n (%)	81 (19.9%)	29 (18.8%)	9 (20.0%)	7 (13.7%)	11 (16.2%)	25 (27.8%)	.24
Had weight gain, n (%)	34 (8.4%)	12 (7.8%)	2 (4.5%)	7 (13.5%)	2 (3.1%)	11 (12.4%)	.14

Table 2 continued.

Characteristic	All patients, n=412	Persistent good sleep, n=155 (37.6%)	Good sleep, worsening, n=45 (10.9%)	Alternating sleep quality, n=54 (13.1%)	Poor sleep, improving, n=68 (16.5%)	Persistent poor sleep, n=90 (21.8%)	p-value[a]
Depression symptoms[b]							
HADS-D score, mean (SD)	3.4 (3.3)	2.4 (3)*,†	3.3 (3)	3.2 (3)	4.3 (4)*	4.5 (3)†	<.001
HADS-D > 7	57 (13.9%)	12 (7.8%)*	5 (11.1%)	8 (15.4%)	13 (19.1%)	19 (21.1%)*	.03
Anxiety symptoms							
HADS-A score, mean (SD)	5.4 (3.8)	3.8 (3) *,†,‡	6.1 (3)*	4.6 (3)§	6.4 (4) †	7.3 (4)‡,§	<.001
HADS-A > 7	109 (26.7%)	19 (12.3%)*,†	12 (26.7%)	9 (17.3%)‡	25 (37.3%)*	44 (48.9%)†,‡	<.001

*, †, ‡, and § describes pairwise comparison within a row. Statistically significant (p<0.01) differences are denoted with similar symbols. Statistical significance was adjusted by the Bonferroni post-hoc correction for multiple comparisons.

[a] P values obtained from comparison statistics: Chi-square test for categorical variables and t-test for normally distributed continuous variables.

[b] There were 21 missing values on education level, 20 on living arrangements, 2 up to 8 on each coping style, 14 on comorbidity score, 3 up to 30 on HNC symptoms, 3 on depression symptoms, and 4 on anxiety symptoms.

[c] Living together includes living with partner and/or children, living in institution, or living with relatives

[d] Performance status as measured with the eastern cooperative oncology group (ECOG) performance status, higher score means worse physical performance.

[e] Oropharynx cancer includes 82 patients (20%) with HPV-positive, 38 (9%) HPV-negative, and 24 (6%) unknown HPV status.

[f] Patients with unknown primary tumor were not included in the comparison statistics due to small sample size.

[g] Other treatment combination consist of radiotherapy with hyperthermic therapy.

[h] Only 2 patients (0.5%) used feeding tube at baseline, thus this outcome was not compared among trajectories.

Abbreviations: HNC, head and neck cancer; HADS-A, hospital anxiety and depression scale anxiety subscale; HADS-D, hospital anxiety and depression scale depression subscale; HPV, human papilloma virus; IQR, interquartile range; NA, Not applicable; PSQI, Pittsburgh sleep quality index; SD, standard deviation.

Sleep quality status over time

The mean (SD) of PSQI total scores at baseline, M3, and M6 were 5.5 (3.6), 5.8 (4), and 5.2 (3.7), respectively. Using a PSQI cut-off score of > 5, poor sleep quality was found among 177 patients (43.0%) at baseline, 183 patients (44.4%) at M3, and 154 patients (37.4%) at M6. Regarding sleep quality trajectories, the majority of the patients remained stable: 155 patients (37.6%) had persistent good sleep and 90 patients (21.8%) had persistent poor sleep. The remaining patients changed over time: 45 patients (10.9%) had worsened sleep quality, 68 patients (16.5%) had improved sleep quality, and 54 patients (13.1%) alternated between good and poor sleep over time (Figure 1).

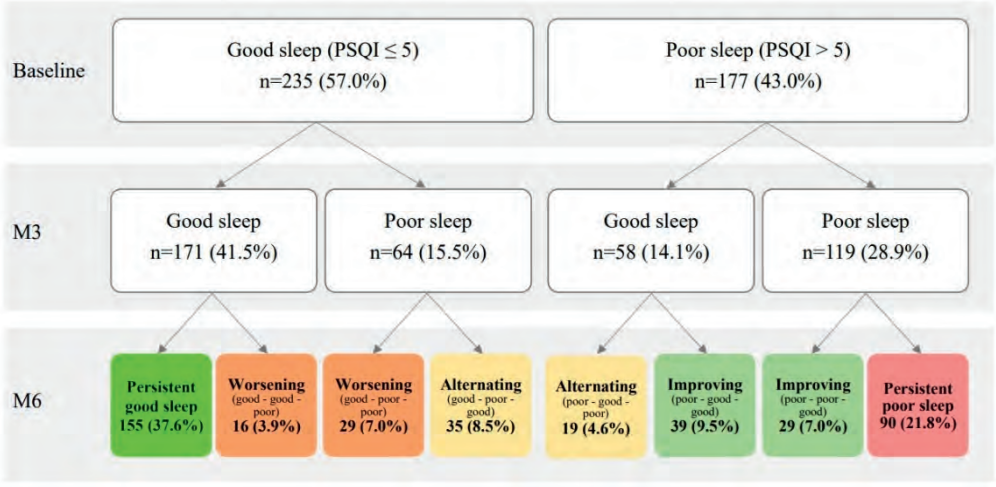

Figure 1 Sleep quality at baseline, 3-month, and 6-month after treatment**. Abbreviations:** PSQI, Pittsburgh sleep quality index.

Determinants of sleep quality trajectories

Univariate analyses (Table 2) showed that patients in the different trajectories of sleep quality differed in sex (P<.001), the extent of passive coping (P<.001), pretreatment painkiller use (P<.001), and the extent of several symptoms: oral pain (P=0.02), swallowing problems (P=0.046), problems with social eating (P=0.001), less sexuality interest and enjoyment (P<.001), feeling ill (P<.001), depression symptoms (P<.001), and anxiety symptoms (P<.001). These variables had a low collinearity (VIF < 2.2); therefore, all variables were included in the multivariable multinomial logistic regression analysis. Forward-stepwise selection retained sex (P=0.02), problems with social eating (P =0.03), use of painkillers (P=0.03), and anxiety symptoms (P <.001) in the final model (Table 3). Women (compared to men, odds ratio [OR] =1.98, 95%

confidence interval [CI] 1.01 to 3.90) and patients who used painkillers at baseline (compared to not using painkillers, OR=2.52, 95% CI 1.33 to 4.77) were more likely to be persistent poor sleepers than to be persistent good sleepers. Patients with more problems with social eating at baseline (OR=1.37, 95% CI 1.12 to 1.69) were more likely to have poor sleep at baseline which improved over time than to be persistent good sleepers. Patients with more anxiety symptoms at baseline were more likely to have poor sleep at baseline which improved (OR=1.22, 95% CI 1.12 to 1.34) or persisted over time (OR=1.26, 95% CI 1.15 to 1.38), or to have good sleep at baseline which worsened over time (OR=1.22, 95% CI 1.09 to 1.36) than to have persistent good sleep.

Table 3 Odds ratios (95% confidence intervals) and *P*-values of baseline characteristics among different trajectories of sleep quality, using persistent good sleep (n=147, 38.8%) as reference outcome.

Characteristic	Good sleep, worsening n=41 (10.8%)	Alternating sleep quality n=46 (12.1%)	Poor sleep, improving n=64 (16.9%)	Persistent poor sleep n=81 (21.4%)	P value
Female (reference: male)	0.54 (0.20 to 1.49)	0.61 (0.23 to 1.64)	1.45 (0.69 to 3.06)	1.98 (1.01 to 3.90)	.02
Problems with social eating (per 10 point increase)	1.11 (0.86 to 1.44)	1.23 (0.97 to 1.56)	1.37 (1.12 to 1.69)	1.13 (0.91 to 1.39)	.03
Used painkillers (reference: not using painkillers)	1.89 (0.88 to 4.07)	1.12 (0.54 to 2.33)	1.03 (0.52 to 2.01)	2.52 (1.33 to 4.77)	.03
Anxiety symptoms (per 1 point increase)	1.22 (1.09 to 1.36)	1.10 (0.99 to 1.22)	1.22 (1.12 to 1.34)	1.26 (1.15 to 1.38)	<.001

Analysis was performed with complete case approach (N=379).

Discussion

We aimed to examine sleep quality trajectories among HNC patients from cancer diagnosis up to six months after treatment, using data from a multicenter prospective cohort in the Netherlands. Of all included patients, 43% had poor sleep before starting HNC treatment, which is higher than the prevalence of poor sleep quality in general population (37%) [12]. At three and six months after HNC treatment, the prevalence of poor sleep quality was 44% and 37%, respectively. Almost half of the HNC patients were either persistent good sleepers or initially poor sleepers with improving sleep over time. About a third were persistent poor sleepers, or initially good sleepers with worsening sleep over time. The remaining patients alternated between good and poor sleep.

The second aim of this study was to identify risk factors of unfavorable sleep trajectories over time. Sex, use of painkillers, anxiety, and social eating problems appeared to be relevant risk factors. First, female HNC patients were more likely than males to have persistent poor sleep than to have persistent good sleep. In the general population, women are more vulnerable than men to have persistent poor sleep after experiencing distress [21]. In addition, two systematic reviews concluded that being female is a risk factor of having poor sleep both among general population across all ages [22] and among older adults [23]. Our finding confirmed earlier studies among HNC patients that poor sleep quality one year after diagnosis was associated with being female, younger, unmarried, as well as having more depressive symptoms before start of treatment [5, 6]. However, we did not find an association between age nor marital status and sleep quality trajectories. Also, we did not find an independent association between depressive symptoms and sleep quality trajectories. Instead, HNC patients with a higher level of anxiety symptoms at baseline were more at risk to have poor sleep before treatment which either persisted or improved over time, or good sleep before treatment which worsened over time. Although anxiety, depression, and poor sleep among cancer patients often co-occur at the same time in the psycho-neurological symptom cluster [24], the presence of one symptom may precede the other [25, 26]. Moreover, anxiety symptoms among HNC patients may also display different trajectories, as already reported in other cancer populations [27, 28]. More research is needed to confirm whether anxiety and depressive symptoms after HNC treatment are also associated with certain sleep quality trajectories.

Furthermore, HNC patients who used painkillers before start of cancer treatment had a higher risk to be persistent poor sleepers. Pain is a common problem among HNC patients: a meta-analysis found that 57% of HNC patients report pain before starting treatment [29] and half of all HNC patients in our study used painkillers before treatment. Although common over-the-counter painkillers, such as acetaminophen, ibuprofen, and aspirin, are known to improve poor sleep quality caused by pain, more potent painkillers such as opioids may disturb sleep quality through its effect on sleep-wake regulation [30]. Opioids are often prescribed among newly-diagnosed HNC patients; a study among Canadian HNC patients reported 38% of patients were prescribed opioids before starting treatment [31]. Moreover, HNC patients who use opioid before treatment are three times more likely to continue using opioid until six months after treatment [32]. More research is needed to confirm whether a long-term use of opioids contribute to persistent sleep disturbances among HNC patients, and ultimately, to investigate adequate pain management which does not impact their sleep quality.

Finally, we found that HNC patients who had more problems with social eating at baseline had a higher risk of having poor sleep before treatment which improved over time. In the Netherlands, dietary guidance for HNC patients is initiated as cancer

treatment starts [33], which may help to resolve their eating problems, improving health in general, and also their sleep quality over time. Future research is needed to examine whether problems with the functional aspect of eating (e.g. oral dysfunction or dysphagia), which often arises after the treatment starts [34], impairs sleep trajectories in the longer term.

A strength of our study is that a large number of HNC patients was examined in this multi-center study, starting from HNC diagnosis to six months after treatment. Another strength is that we examined different trajectories of sleep quality over-time, instead of merely examining mean change of sleep quality scores over-time. Our study has also some limitations. First, the excluded participants (i.e., patients who died or dropped-out before M6 and participants who had missing PSQI score on at least one time-point) were more likely to have low education level, live alone, have worse performance status, and worse comorbidity. As these variables were found to be associated with the less favorable sleep trajectories [35, 36], our results may underrepresent those who had worse sleep quality trajectories. Further research is needed to explore whether this patient group has more risk to have persistent poor sleep and other negative events in a longer term (e.g., suicide, relationship problems). Second, we did not examine whether HNC patients already had a history of poor sleep before being diagnosed with HNC, which may be a relevant predisposing factor of having persistent poor sleep later on. Third, we did not take into account the extent of HNC and psychological symptoms at 3 and 6 months after treatment on sleep quality trajectories. These post-treatment symptoms may also affect sleep quality trajectories.

In conclusion, approximately half of the HNC patients had persistent good sleep quality or their sleep quality improved from pre-treatment to 6 months after treatment. Over a third had persistent poor sleep or developed poor sleep quality. A minority had alternating sleep quality over time. Patients at risk for persistent poor sleep quality are women, those who use pain killers, or those with higher symptoms of anxiety as measured pre-treatment. A periodic sleep evaluation starting at pre-treatment is necessary to identify persistent sleep problems, especially among the high-risk groups. A (digital) validated sleep questionnaire can serve as a useful tool since it can be administered shortly before the follow-up appointments with the treating surgeon or with the general practitioner.

References

1. Santoso AM, Jansen F, de Vries R, Leemans CR, van Straten A, Verdonck-de Leeuw IM. Prevalence of sleep disturbances among head and neck cancer patients: a systematic review and meta-analysis. Sleep medicine reviews. 2019;47:62-73.
2. Angelina M, Femke J, Birgit I, Robert J, Johannes AL, Johannes HS, et al. Poor Sleep Quality Among Newly Diagnosed Head and Neck Cancer Patients: Prevalence and Associated Factors. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer.
3. Hu Z-y, Feng X-q, Fu MR, Yu R, Zhao H-l. Symptom patterns, physical function and quality of life among head and neck cancer patients prior to and after surgical treatment: A prospective study. European Journal of Oncology Nursing. 2020:101770.
4. Davis MP, Goforth HW. Long-term and short-term effects of insomnia in cancer and effective interventions. The Cancer Journal. 2014;20(5):330-44.
5. Duffy SA, Khan MJ, Ronis DL, Fowler KE, Gruber SB, Wolf GT, et al. Health behaviors of head and neck cancer patients the first year after diagnosis. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 2008;30(1):93-102.
6. Shuman AG, Duffy SA, Ronis DL, Garetz SL, McLean SA, Fowler KE, et al. Predictors of poor sleep quality among head and neck cancer patients. The Laryngoscope. 2010;120(6):1166-72.
7. Veldhuis D, Probst G, Marek A, Noack V, Ural A, Adamietz I, et al. Tumor site and disease stage as predictors of quality of life in head and neck cancer: a prospective study on patients treated with surgery or combined therapy with surgery and radiotherapy or radiochemotherapy. European Archives of Oto-Rhino-Laryngology. 2016;273(1):215-24.
8. Verdonck-de Leeuw I, Jansen F, Brakenhoff R, Langendijk J, Takes R, Terhaard C, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. BMC cancer. 2019;19(1):1-13.
9. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213.
10. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. Journal of pain and symptom management. 2004;27(2):140-8.
11. Tzeng JI, Fu Y-W, Lin C-C. Validity and reliability of the Taiwanese version of the Pittsburgh Sleep Quality Index in cancer patients. International journal of nursing studies. 2012;49(1):102-8.
12. Hinz A, Glaesmer H, Brähler E, Löffler M, Engel C, Enzenbach C, et al. Sleep quality in the general population: psychometric properties of the Pittsburgh Sleep Quality Index, derived from a German community sample of 9284 people. Sleep medicine. 2017;30:57-63.
13. Piccirillo J, Costas I, Claybour P, Borah A, Grove L, Jeffe D. The measurement of comorbidity by cancer registries. J Registry Manage. 2003;30(1):8-15.
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-56.
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.
16. Schreurs P, Van de Willige G, Brosschot J, Tellegen B, Graus G. De Utrechtse Coping Lijst (Utrecht Coping Questionnaire). Lisse: Swets and Zeitlinger; 1993.
17. Hoekstra-Weebers JE, Wijnberg-Williams BJ, Jaspers JP, Kamps WA, van de Wiel HB. Coping and its effect on psychological distress of parents of pediatric cancer patients: a longitudinal prospective study. Psycho-Oncology. 2012;21(8):903-11.

18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica. 1983;67(6):361-70.
19. Vodermaier A, Linden W, Siu C. Screening for emotional distress in cancer patients: a systematic review of assessment instruments. Journal of the National Cancer Institute. 2009;101(21):1464-88.
20. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Supportive Care in Cancer. 2011;19(12):1899.
21. Palagini L, Bruno RM, Paolo T, Caccavale L, Gronchi A, Mauri M, et al. Association between stress-related sleep reactivity and metacognitive beliefs about sleep in insomnia disorder: preliminary results. Behavioral sleep medicine. 2016;14(6):636-49.
22. Zhang B, Wing Y-K. Sex differences in insomnia: a meta-analysis. Sleep. 2006;29(1):85-93.
23. Smagula SF, Stone KL, Fabio A, Cauley JA. Risk factors for sleep disturbances in older adults: evidence from prospective studies. Sleep medicine reviews. 2016;25:21-30.
24. Miaskowski C, Barsevick A, Berger A, Casagrande R, Grady PA, Jacobsen P, et al. Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. JNCI: Journal of the National Cancer Institute. 2017;109(4).
25. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. Sleep. 2013;36(7):1059-68.
26. Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rössler W. Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep. 2008;31(4):473-80.
27. Dunn LB, Aouizerat BE, Cooper BA, Dodd M, Lee K, West C, et al. Trajectories of anxiety in oncology patients and family caregivers during and after radiation therapy. European Journal of Oncology Nursing. 2012;16(1):1-9.
28. Lam W, Soong I, Yau T, Wong K, Tsang J, Yeo W, et al. The evolution of psychological distress trajectories in women diagnosed with advanced breast cancer: a longitudinal study. Psycho-Oncology. 2013;22(12):2831-9.
29. Macfarlane TV, Wirth T, Ranasinghe S, Ah-See KW, Renny N, Hurman D. Head and neck cancer pain: systematic review of prevalence and associated factors. Journal of oral & maxillofacial research. 2012;3(1).
30. Van Gastel A. Drug-induced insomnia and excessive sleepiness. Sleep medicine clinics. 2018;13(2):147-59.
31. Henry M, Alias A, Frenkiel S, Richardson K, Hier M, Zeitouni A, et al. Contribution of psychiatric diagnoses to extent of opioid prescription in the first year post-head and neck cancer diagnosis: A longitudinal study. Psycho-Oncology. 2019;28(1):107-15.
32. Cata JP, Patino M, Gorur A, Du KN, Uhelski ML, Myers J, et al. Persistent and Chronic Postoperative Opioid Use in a Cohort of Patients with Oral Tongue Squamous Cell Carcinoma. Pain Medicine. 2020;21(5):1061-7.
33. Leistra E, Eerenstein SE, van Aken LH, Jansen F, de van der Schueren MA, Twisk JW, et al. Effect of early individualized dietary counseling on weight loss, complications, and length of hospital stay in patients with head and neck cancer: a comparative study. Nutrition and cancer. 2015;67(7):1093-103.
34. Larsson M, Hedelin B, Johansson I, Athlin E. Eating problems and weight loss for patients with head and neck cancer: a chart review from diagnosis until one year after treatment. Cancer nursing. 2005;28(6):425-35.
35. Wang Y, Zhu X, Li L, Yi J, He J. What Factors Affect the Insomnia Symptom Trajectories in Women With Nonmetastatic Breast Cancer? Journal of pain and symptom management. 2016;52(6):850-8.
36. Van Onselen C, Cooper BA, Lee K, Dunn L, Aouizerat BE, West C, et al. Identification of distinct subgroups of breast cancer patients based on self-reported changes in sleep disturbance. Supportive Care in Cancer. 2012;20(10):2611-9.

Chapter V

Psychoneurological symptoms and biomarkers of stress and inflammation in newly diagnosed head and neck cancer patients: a network analysis

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Abstract

Psychoneurological symptoms are commonly reported by newly diagnosed head and neck cancer (HNC) patients, yet there is limited research on the associations of these symptoms with biomarkers of stress and inflammation. In this article, pre-treatment data of a multi-center cohort of HNC patients was analyzed using network analysis to examine connections between symptoms (poor sleep quality, anxiety, depression, fatigue, and oral pain), biomarkers of stress (diurnal cortisol slope), inflammation markers (c-reactive protein [CRP], interleukin [IL]-6, IL-10, tumor necrosis factor alpha [TNF-α]), and covariates (age and body mass index [BMI]). Three centrality indices were calculated: degree (number of connections), closeness (proximity of a variable to other variables), and betweenness (based on the number of times a variable is located on the shortest path between any pair of other variables). In the sample of 264 patients, poor sleep quality and fatigue had the highest degree index, fatigue and CRP had the highest closeness index, and IL-6 had the highest betweenness index. The model yielded two clusters: a symptoms – cortisol slope – CRP cluster and a IL-6 – IL-10 – TNF-α – age – BMI cluster. Both clusters were connected most prominently via IL6. Our findings provide evidence that poor sleep quality, fatigue, CRP, and IL-6 play an important role in the interconnections between psychoneurological symptoms and biomarkers of stress and inflammation in newly diagnosed HNC patients.

Introduction

Head and neck cancers (HNC) include a range of cancers located in the nasal cavity, paranasal sinuses, oral cavity, pharynx, larynx, and salivary glands. Every year, more than 550,000 people in the world are newly diagnosed with HNC[1]. The period between diagnosis of HNC and start of treatment is often stressful. Patients usually present to the healthcare facilities with orofacial pain, swallowing problems, neck lump, hoarseness, or weight loss[2]. Besides dealing with cancer symptoms and multiple diagnostic procedures, HNC patients are often anxious about disease prognosis and the effect of cancer treatment on their daily life [3]. Newly diagnosed HNC patients often report not only pain (especially in the mouth and neck area)[4] but also poor sleep quality[5], psychological distress[6], and fatigue [7]. These symptoms often co-occur in cancer patients and they are often referred to as 'psychoneurological symptoms' [8, 9].

It is hypothesized that psychoneurological symptoms are related to biomarkers of stress and inflammation. Cortisol, a stress-related hormone produced in the hypothalamic-pituitary-adrenal (HPA) axis, plays an important role in the regulation of metabolism, cardiovascular system, and inflammation response [10]. Under normal circumstances, the concentration of cortisol follows a diurnal rhythm: it is high at waking up, increases rapidly until it peaks within 30-45 minutes after awakening, then decreases steadily towards its lowest level around midnight [11]. This normal fluctuation is found to be altered upon stress, e.g. in the presence of psychoneurological symptoms: the cortisol peak shifts to a later timepoint or completely disappears, showing a blunted or flatter diurnal cortisol slope [12]. Such diurnal rhythm disruption (i.e., flatter diurnal cortisol slope) is found to be associated with higher inflammatory markers[13]. Higher inflammation is hypothesized to involve HNC progression by stimulating cancer proliferation, migration, and angiogenesis [14].

Previous studies in newly diagnosed lung, ovarian, and colorectal cancer patients suggested associations between: 1) worse sleep quality and flatter cortisol slope [15] and 2) worse psychoneurological symptoms (i.e., poor sleep quality, anxiety, depression, and fatigue) and higher inflammation markers [16-18]. In newly diagnosed HNC patients specifically, significant associations were demonstrated between fatigue and higher levels of inflammation markers interleukin-6 (IL-6) and c-reactive protein (CRP) [19], and between pain and a higher level of CRP [20]. To the best of our knowledge, no study has investigated associations between psychoneurological symptoms, cortisol, and inflammatory markers altogether in newly diagnosed HNC patients. This information is needed to understand the pathophysiology of psychoneurological symptoms in newly diagnosed HNC patients and eventually to design a better monitoring and intervention strategy for these symptoms.

Psychoneurological symptoms and biomarkers of stress and inflammation may influence each other by providing positive or negative feedback [21, 22]. Hypothetically, the association between two specific elements (i.e. a specific symptom or a biomarker) may also be influenced by their associations with the other remaining elements. Network analysis takes this complexity into account and it is used increasingly in mental health research [23]. Therefore, we used this novel approach to examine the associations between psychoneurological symptoms (poor sleep quality, anxiety, depression, fatigue, and oral pain), and biomarkers of stress (diurnal cortisol slope) and inflammation (CRP, IL-6, interleukin-10 [IL-10], and tumor necrosis factor alpha [TNF-α]) among newly diagnosed HNC patients. Based on the available literature, we expected positive connections between psychoneurological symptoms and inflammation markers (i.e., worse symptoms are associated with higher inflammation markers) [16-20], and negative connections between cortisol slope with psychoneurological symptoms and inflammation markers (i.e., flatter cortisol slope is associated with worse psychological symptoms and with higher inflammation markers) [13, 15].

Patients and Methods

2.1. Study population

Baseline data from the ongoing NETherlands Quality of Life and Biomedical Cohort study in head and neck cancer (NET-QUBIC) was used [24]. From March 2014 to June 2018, all HNC patients who were newly diagnosed at 5 university hospitals and 3 satellite hospitals were assessed for their eligibility to participate in the study. The study was approved by the Medical Ethical Committee of the VU University Medical Center Amsterdam (2013.301(A2018.307)-NL45051.029.13).

Descriptive characteristics were obtained as follows. Sex, age, and clinical characteristics (HNC subsite, HNC stage, performance status, and comorbidity) were obtained from electronic medical records. Education level and living situation were obtained from interview or questionnaires. Smoking status (smoking daily at baseline) and excessive alcohol consumption (>14 units of alcohol per week for women or >21 units of alcohol per week for men) were self-reported using a study-specific questionnaire. BMI was calculated based on height and weight (weight [kg]/height [m]^2), which were measured using a standardized procedure during a home visit. Among these characteristics, two continuous variables were included in the network model as covariates as they are associated with higher inflammatory markers, namely age [25] and BMI [26].

2.2. Inclusion and exclusion criteria of NET-QUBIC study

Inclusion criteria were: 18 years or older; diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, or neck lymph node metastasis of an unknown primary tumor; intention of curative treatment; and able to write, read, and speak Dutch. Exclusion criteria were severe psychiatric comorbidity (e.g., schizophrenia, Korsakoff's syndrome, severe dementia) as participation in the study was thought to be too burdensome. In addition, patients with less prevalent types of HNC (i.e., lymphoma, thyroid cancer, nasopharyngeal cancer, malignancy of skin, or malignancy of salivary glands) were excluded from the study.

2.3. Measures

NET-QUBIC encompasses measurements at baseline (before start of treatment) and at 3, 6, 12, 24, 36, 48, and 60 months follow-up. In this study, we used only the baseline measurements.

Sleep quality was measured using the Pittsburgh sleep quality index (PSQI) [27]. Its validity and reliability have been confirmed in cancer patients [28]. PSQI covers seven domains of sleep quality and disturbances [27], each domain score ranges from 0 to 3. The PSQI total score ranges from 0 to 21; a higher score indicates poorer sleep quality.

Psychological distress, i.e. depression and anxiety symptoms, was assessed using the 14-item hospital anxiety and depression scale (HADS) [29]. The anxiety (HADS-A) and depression (HADS-D) subscales both consist of 7 items, each ranges from 0 to 3. The sum score of each subscale ranges from 0 to 21; a higher score indicates a higher extent of depression or anxiety symptoms. The HADS is demonstrated to have good psychometric properties in measuring anxiety and depression among cancer patients [30].

Pain was measured using the oral pain subscale of the European organization for research and treatment of cancer quality of life questionnaire, HNC specific module (EORTC QLQ- H&N35) [31]. This subscale consists of 4 items on whether the patient has had pain in the mouth, jaw, or throat, or soreness in the mouth (further referred to as oral pain). The subscale score ranges from 0 to100; a higher score indicates worse extent of oral pain [32].

Fatigue was measured using the general fatigue scale of the Multidimensional Fatigue Inventory (MFI-20) [33]. This scale consists of four items, each item is scored on a 5-point Likert scale, yielding a summary score which ranges from 4 (least fatigued) to 20 (most fatigued). This scale has good psychometric properties in measuring fatigue among cancer patients [33].

Saliva collection and cortisol measurement were performed as follows. Patients were instructed to collect saliva at four time points: at awakening, 30 minutes after awakening, 60 minutes after awakening, and at 22:00. Patients were given 4 salivette tubes (one for each saliva collection) and were instructed to note the exact time of saliva collection. All samples were collected at home by the patients after thorough explanation by trained fieldworker (along with a written guideline) and sent by mail to the coordinating research center (Amsterdam UMC, location VUmc). Upon receipt, the samples were immediately centrifuged, transferred to storage vials, and stored at -20 ºC. Saliva cortisol concentrations were measured at the Endocrine Laboratory of the Amsterdam UMC, location AMC with the use of an isotope dilution LC-MS/MS method. In short, internal standard (13C3-labeled cortisol, Isosciences) was added to the samples. Samples were extracted by supported liquid extraction (Biotage) and analysed on a LC-MS/MS (Xevo TQ-S Micro LC-MS-MS System, Waters Corporation). The lower limit of quantitation was 1.0 nmol/L. The intra-assay variation was 5% and 3% at cortisol concentrations of 2 and 15 nmol/L, respectively. The inter-assay variation was <9% over the whole concentration range. Diurnal cortisol slope was calculated by substracting cortisol level at 22:00 from cortisol level at awakening, divided by the duration (in hours) between these two time-points [34]. A higher value of slope means a steeper decline of cortisol, a lower value of slope means a slower decline, and a negative slope indicates an increasing cortisol level during the day.

Inflammatory markers (CRP, IL-6, IL-10, TNF-α) were measured from venous blood samples collected by a research nurse or trained fieldworker. For CRP, blood was collected in a heparine-gel tube. CRP was immediately determined in the laboratories of the participating hospitals according to standard laboratory protocol. For cytokines IL-6, IL-10, and TNF-α, blood was collected in tube for serum collection with a clot activator. The serum samples were preprocessed according to the standard laboratory protocol and stored at NET-QUBIC biobank (AmsterdamUMC, location VUmc) at -80 ºC until the day of the assay. Cytokines were measured by the laboratory of Clinical Chemistry at AmsterdamUMC, location VUmc in 500 µl aliquots. Each sample was analyzed using an ELISA based technology that uses electrochemiluminescence for detection with Meso Scale Discovery Quickplex SQ 120 Imager (cat. # K15049-Series, Meso Scale Discovery, Rockville MD). The intraassay variations were 4.7% (IL-6), 4.0% (IL-10) and 3.7% (TNF-α) and the interassay variations were 7.9% (IL-6), 5.5% (IL-10), and 8.0% (TNF-α).

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS (IBM Corp., Armonk, NY USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Sociodemographic factors, clinical characteristics, smoking and alcohol use, psychoneurological symptoms, and biomarkers were compared between patients with complete versus incomplete data: chi-square test for categorical variables, unpaired t-test for normally distributed continuous variables or Mann-Whitney U test for non-normally distributed variable. Statistical significance was defined as p-value < 0.05. We adjusted for multiple testing by controlling the false discovery rate (FDR) [35].

An undirected network model was estimated to examine the connections between poor sleep quality, symptoms of anxiety, symptoms of depression, oral pain, fatigue, biomarkers (cortisol slope, CRP, IL-6, IL-10, and TNF-α), and covariates (age and BMI). Only participants with complete data for these 12 variables were included in the analyses (i.e., listwise approach). The network model was estimated using R package *Rags2Ridges* version 2.2.3 [36]. First, skewed distributions were normalized using non-paranormal transformations using *huge.npn* function from the *huge* package . Network extraction was then based on targeted ridge estimation of the partial correlation matrix [37]. The resulting partial correlation matrix was sparsified by thresholding, choosing an absolute value ≥ .1 as the cut-off value. The resulting networks are conditional independence graphs. In such graphs the nodes represent the variables (i.e., symptoms, biomarkers, and covariates) and the connections between node-pairs represent a substantive partial correlation, i.e., an association that cannot be conditioned away by the remaining nodes (given the chosen threshold). The network of conditional associations was visualized using the Fruchterman-Reingold approach, which locates highly associated nodes closer to each other [38]. To gain insight into the structural importance of the nodes in the network, we calculated three centrality indices, namely "degree" (the number of connections for a node),"closeness" (average proximity of a node to all other nodes), and "betweenness" (based on the number of times a node is located on the shortest path between any pair of other nodes) [39]. Finally, we examined the clustering of nodes (i.e., variables which are closer to each other) using the edge betweenness approach, also known as shortest-path betweenness [40].

Results

3.1. Study population

Given the large scope of the study measurements, at baseline, the newly diagnosed NET-QUBIC participants were given the possibility to participate only in certain components of the assessment (i.e., questionnaires, home-based tests, self-collected saliva, and/or blood collection). In this study, using 12 variables of interest, missing values ranged from one variable (in 141 patients) to 11 variables (in 20 patients). The most missing values were found for cortisol slope (46%), sleep quality (24%), fatigue (24%), BMI

(23%), anxiety (19%), and depression (19%). Among all 739 patients included in the NET-QUBIC study, 264 patients (36%) had complete data on all twelve variables of interest and were included in the network analysis.

Table 1 provides an overview of characteristics of patients with complete (n=264) versus those with incomplete data (n=475). Patients with complete data were older (mean age 65 years [SD=8.2] versus 62 years [SD=10.4], adjusted p=0.007), more often lived together with family or relatives (81.4% versus 70.1%, adjusted p=0.007), and were less fatigued (median=9.0 [5.0 – 13.0] versus 11.5 [6.0 – 14.0], adjusted p=0.007). No statistically signifi-cant difference was found for clinical characteristics, biomarkers, daily smoking status, and excessive alcohol consumption.

Table 1. Characteristics of patients with complete data (the study population) versus patients with incomplete data.

Characteristics	Patients with complete data (n=264)	Patients with incomplete data (n=475)	Adjusted p-value[a]
Age (mean, SD)	65 (8.2)	62 (10.4)	0.007
Men, No. (%)	209 (79.2%)	340 (71.6%)	0.112
Education level, No. (%)[b]			
Low	107 (40.5%)	172 (44.8%)	0.560
Middle	77 (29.2%)	94 (24.5%)	
High	80 (30.3%)	118 (30.7%)	
Living together, No. (%)[b]	215 (81.4%)	270 (70.1%)	0.007
HNC location, No. (%)			
Oral cavity	64 (24.2%)	135 (28.4%)	0.427
Oropharynx	98 (37.1%)	164 (34.5%)	
Hypopharynx	17 (6.4%)	35 (7.4%)	
Larynx	81 (30.7%)	124 (26.1%)	
Unknown primary	4 (1.5%)	17 (3.6%)	
HNC stage, No. (%)			
I	67 (25.4%)	96 (20.2%)	0.559
II	48 (18.2%)	84 (17.7%)	
III	40 (15.2%)	87 (18.3%)	
IV	109 (41.3%)	208 (43.8%)	
ECOG performance status, No. (%)			
0	191 (72.3%)	316 (66.5%)	0.238
1 or more	73 (27.7%)	159 (33.5%)	
Comorbidity, No. (%)[b]			
None	86 (33.7%)	118 (26.6%)	0.427
Mild	93 (36.5%)	171 (38.5%)	
Moderate	51 (20%)	104 (23.4%)	
Severe	25 (9.8%)	51 (11.5%)	
Excessive alcohol consumption, No. (%)[b]	58 (22.0%)	71 (22.8%)	0.805
Smoking daily, No. (%)[b]	57 (21.7%)	70 (22.7%)	0.805
BMI (kg/m^2)[b], mean (SD)	26.1 (4.5)	25.3 (4.6)	0.112
Sleep (PSQI score)[b], median (IQR)	5.0 (3.0 - 7.0)	5.0 (3.0 – 9.0)	0.600
Depression (HADS-D score)[b], median (IQR)	3.0 (1.0 – 6.0)	3.0 (1.0 – 6.0)	0.791
Anxiety (HADS-A score)[b], median (IQR)	5.0 (3 .0 - 7.8)	5 (3.0 – 8.0)	0.600
Oral pain (EORTC-H&N35)[b], median (IQR)	16.7 (8.3 - 33.3)	25 (8.3 – 50.0)	0.112

Table 1 continued.

Characteristics	Patients with complete data (n=264)	Patients with incomplete data (n=475)	Adjusted p-value[a]
Fatigue (MFI general fatigue)[b], median (IQR)	9.0 (5.0 – 13.0)	11.5 (6.0 – 14.0)	0.007
Cortisol slope (nmol/L/hour)[b], median (IQR)	0.47 (0.25 - 0.78)	0.48 (0.28 - 0.77)	0.791
CRP (mg/L)[b], median (IQR)	2.8 (2.5 - 5.5)	3.1 (2.4 - 8.0)	0.238
IL-6 (pg/mL)[b], median (IQR)	1.03 (0.66 - 1.72)	1.11 (0.66 - 1.84)	0.427
IL-10 (pg/mL)[b], median (IQR)	0.24 (0.18 - 0.36)	0.27 (0.19 - 0.40)	0.222
TNF-α (pg/mL)[b], median (IQR)	2.72 (2.32 - 3.37)	2.79 (2.31 - 3.44)	0.600

[a] p-values were obtained from comparison statistics: chi-square test for categorical variables, t-test for normally distributed continuous variables, or Mann-Whitney U test for non-normally distributed variables. Correction for multiple comparison was performed with false discovery rates approach. Statistically significant variables (in bold) was defined by P value < 0.05.

[b] There were 91 missing values on education level, 90 on living arrangements, 40 on comorbidity score, 164 on excessive alcohol consumption, 167 on smoking, 169 on BMI, 179 on PSQI score, 142 on oral pain score, 142 on HADS-D score, 144 on HADS-A score, 177 on MFI general fatigue score, 340 on cortisol slope, 93 on each inflammation markers (CRP, IL-6, IL-10, and TNF- α). Abbreviations: BMI, body mass index; CRP, c-reactive protein; HADS-A, the hospital anxiety and depression scale – anxiety subscale; HADS-D, the hospital anxiety and depression scale – depression subscale; HNC, head and neck cancer; IL, interleukin; IQR, interquartile range; PSQI, Pittsburgh sleep quality index; MFI, multidimensional fatigue inventory; SD, standard deviation; TNF-α, tumor necrosis factor alpha.

3.2. Network analysis

Figure 1 depicts the network of partial correlations between psychoneurological symptoms, biomarkers, and covariates (age and BMI). Solid edges represent positive partial correlations and dashed edges represent negative partial correlations. All edges were positive (indicating that higher levels of symptoms, inflammation markers or covariates were associated with higher levels of other symptoms, inflammation markers or covariates), except for the edge between poor sleep quality and cortisol slope. A higher PSQI total score (poorer sleep quality) was connected with a lower value of cortisol slope (flatter slope).

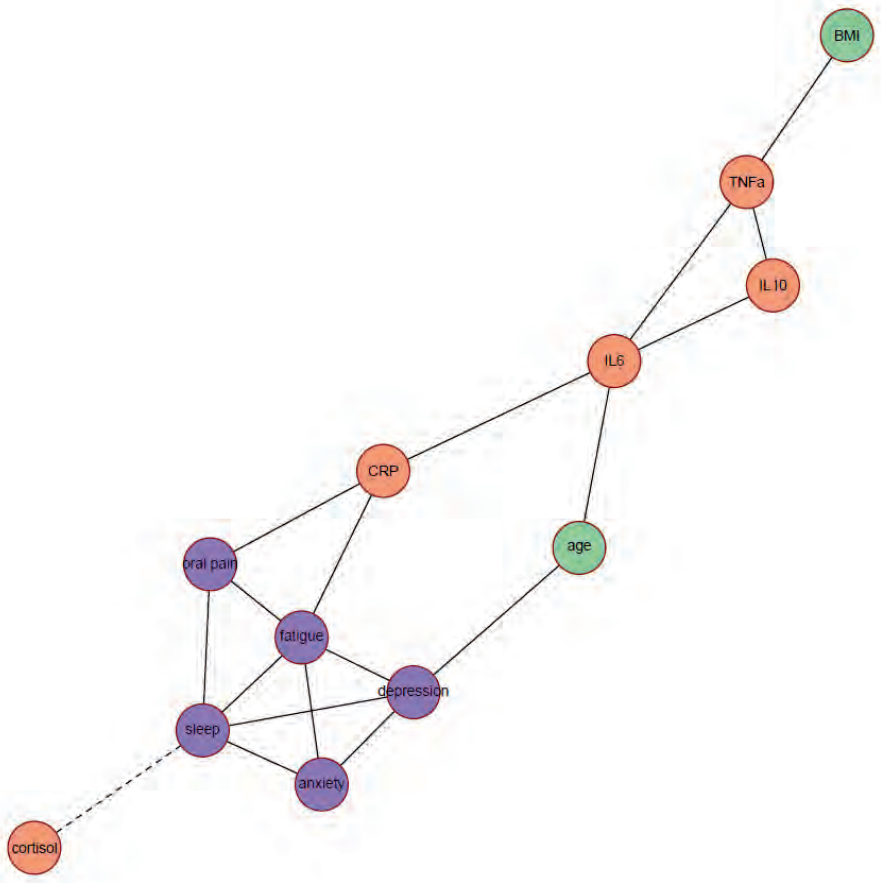

Figure 1 Network displaying the partial correlations between all symptoms (in purple), biomarkers (in salmon orange), and covariates (in green); N=264. Solid edges represent positive partial correlations, dashed edges represent negative partial correlations. Anxiety label indicates HADS anxiety subscale score; depression, HADS depression subscale score; fatigue, MFI general fatigue score; oral pain, EORTC QLQ-H&N35 oral pain subscale score; sleep, PSQI total score; cortisol, diurnal cortisol slope. Abbreviations: BMI, body mass index; CRP, c-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor alpha.

Centrality indices of all nodes are displayed in Table 2. Based on the three centrality indices (degree, closeness, and betweenness), four nodes had the most important position in the network: fatigue (highest degree and closeness), poor sleep quality (highest degree), CRP (highest closeness), and IL-6 (highest betweenness). Poor sleep quality and fatigue were connected with the most number of nodes (i.e., highest degree): each had 5 connections with other nodes. Fatigue and CRP had the highest closeness index, which means that changes in fatigue or CRP will quickly result in changes of any other node in the network, or vice versa. IL-6 had the highest betweenness, which means that IL-6 is most often an intermediate node on the shortest paths between any pair of the nodes. Hence, IL-6 is an important node from the viewpoint of information flow.

Table 2 Centrality indices of the network model.

	Degree	Betweenness	Closeness
Poor sleep quality	5	11.33	0.040
Depression symptoms	4	9.33	0.045
Anxiety symptoms	3	0	0.037
Oral pain	3	3.67	0.042
Fatigue	5	9	0.048
Cortisol slope	1	0	0.028
CRP	3	15.67	0.048
IL-6	4	25.33	0.045
IL-10	2	0	0.033
TNF-α	3	10	0.034
Age	2	8.67	0.043
BMI	1	0	0.026

Anxiety symptoms were measured by HADS anxiety subscale score; depression symptoms, HADS depression subscale score; fatigue, MFI general fatigue score; oral pain, EORTC QLQ-H&N35 oral pain subscale score; poor sleep quality, PSQI total score. Centrality indices are degree (number of connections), closeness (proximity of a variable to other variables), and betweenness (based on the number of times a variable is located on the shortest path between any pair of other variables). Abbreviations: BMI, body mass index; CRP, c-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor alpha.

Two clusters were identified in community analysis (Figure 2). The first cluster consisted of all patient-reported psychoneurological symptoms (poor sleep quality, depres-sion, anxiety, fatigue, and oral pain) together with an inflammation marker (CRP) and stress marker (cortisol slope). The second cluster consisted of the other three inflammation markers (IL-6, IL-10, and TNF-α) and the two covariates (age and BMI). Based on its highest betweenness index, IL-6 was the most important node connecting the two clusters.

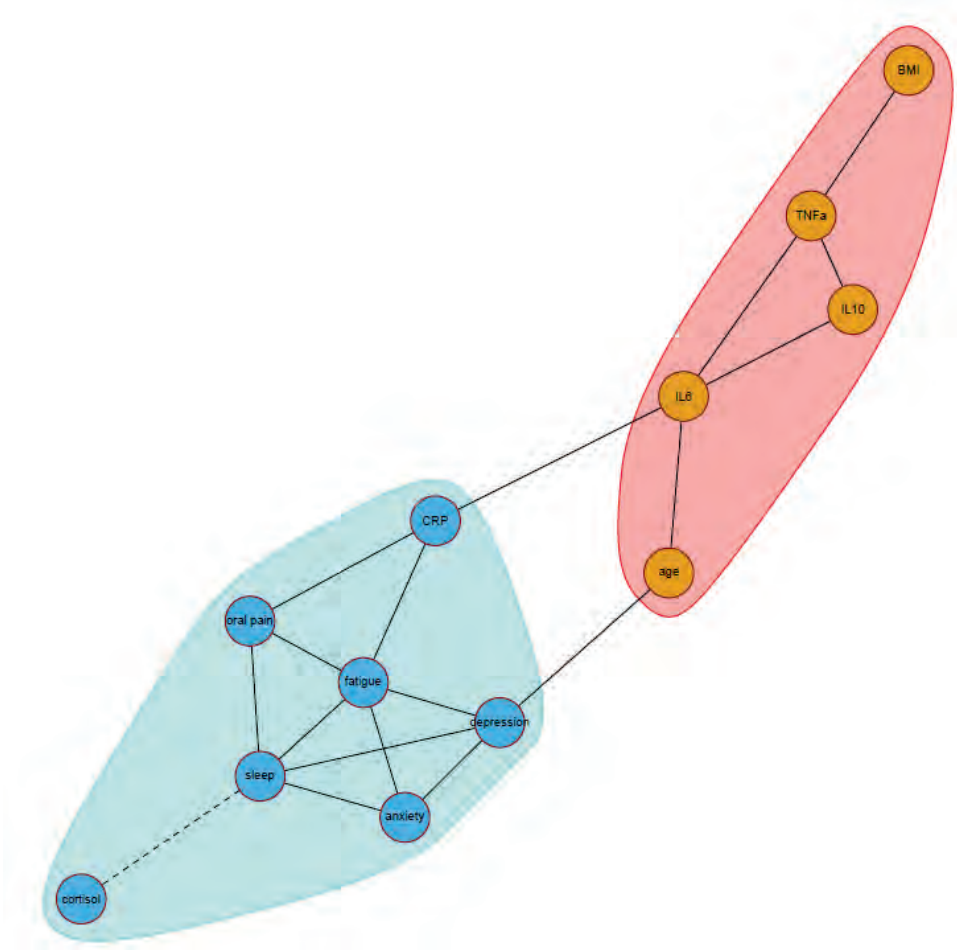

Figure 2 Visualization of community structure between all symptoms, biomarkers, and covariates, using edge betweenness approach (N=264). Solid edges represent positive partial correlations, dashed edges represent negative partial correlations. The two clusters are represented by different colored area (red and blue). Anxiety label indicates HADS anxiety subscale score; depression, HADS depression subscale score; fatigue, MFI general fatigue score; oral pain, EORTC QLQ-H&N35 oral pain subscale score; sleep, PSQI total score; cortisol, diurnal cortisol slope. Abbreviations: BMI, body mass index; CRP, c-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor alpha.

Discussion

To the best of our knowledge, this study is the first to use network analysis to examine associations between psychoneurological symptoms and biomarkers of stress and inflammation in newly diagnosed HNC patients. All psychoneurological symptoms in our network model were connected with each other as well as with biomarkers in the expected directions: worse symptoms were associated with higher levels of inflammatory markers and flattened cortisol slope. Two clusters were identified in our network model: all psychoneurological symptoms – cortisol slope – CRP cluster, and the inflammation cytokines (IL-6, IL-10, TNF-a) – age – BMI cluster. Poor sleep quality, fatigue, CRP, and IL-6 were the most central nodes in the network based on the centrality indices.

The central position of poor sleep quality and fatigue among other psychoneurological symptoms suggesting their importance in the network of psychoneurological symptoms and markers of stress and inflammation. Poor sleep quality may worsen fatigue, anxiety, depression, and lower pain tolerance by impairing emotional regulation [41]. Reciprocally, newly diagnosed HNC patients often suffer from anxiety, depression, fatigue, and oral pain which may disrupt their sleep quality [42]. Fatigue has also been demonstrated both as a cause [43] as well as a consequence [44] of psychological distress and pain in cancer patients. Future study using time-series data is needed to get more insight on the dynamic of these central symptoms in the network model over time.

Based on our network model, IL-6 appeared to be the most important node which connects other non-adjacent nodes, as well as the most important node in terms of information flow between the two clusters. A previous study hypothesized that IL-6 is produced not only by tumor cells to induce HNC proliferation, but also by host cells (e.g., endothelial cells, stromal cells, immune cells) as a response to tumor growth [45]. Furthermore, an accumulative increase of IL-6 induces release of CRP in a larger quantity, a marker of ongoing systemic inflammation [46]. In accordance with previous study in newly diagnosed HNC patients [19], we also found that higher CRP is also associated with worse pain and fatigue.

In this study, the association between stress biomarker and psychoneurological symptoms seemed to take place in particular through the connection of flatter cortisol slope with poor sleep quality. In contrast with earlier findings in general adult population [13], our network model did not indicate a connection between cortisol slope and inflammatory cytokines. This finding may be explained by decreased sensitivity of immune cells towards cortisol (i.e., cortisol resistance) upon systemic inflammation [47], which is hypothesized to play a key role in cancer pathogenesis [48]. A study in HNC patients before and 1 month after treatment found that increasing inflammation and

fatigue was associated with increasing cortisol resistance over time, but this study did not include poor sleep quality in their analysis [49]. Nonetheless, our findings may suggest that poor sleep quality plays an important role in the association between HPA-axis disruption, higher inflammation, and psychoneurological symptoms through several pathways. First, poor sleep quality and flattened cortisol slope may aggravate each other. Second, the cortisol-resistant immune cells may sustain their inflammatory state by ignoring anti-inflammatory cues from cortisol. Both prolonged poor sleep quality and sustained inflammation may lead to more fatigue and eventually worsening the other psychoneurological symptoms. This hypothesis is yet to be tested by further investigation.

A strength of this study is that we examined associations between psychoneurological symptoms, cortisol diurnal slope, and inflammation markers, by network analysis using a large study cohort of newly diagnosed HNC patients. Our findings also need to be interpreted with caution. First, as we analyzed only patients with complete data, our findings may not be fully representative for HNC patients who did not have complete data (those who were younger, lived alone, and were more fatigued). Second, we measured inflammatory marker levels in blood at one time point of the day and these levels may vary throughout the day. However, collecting blood samples multiple times in a day may be too burdensome for the patients. To deal with this issue, future investigations may consider using serial saliva samples to measure inflammatory markers [50]. Third, we only measured IL-6, IL-10 and TNF-α as they were the most frequently studied markers and we did not measure the concentration of other cytokines. A further study including other inflammatory cytokines is needed for a deeper insight on the inflammatory process in the network. Fourth, we did not control for different subgroups of HNC patients, for example based on HNC location or stage. Future study is needed to examine whether the network of psychoneurological symptoms, cortisol diurnal slope and inflammation differ among these sub-populations.

Conclusion

We aimed to investigate the associations of poor sleep quality, depression, anxiety, fatigue, oral pain, and biomarkers of stress and inflammation in newly diagnosed HNC patients. Using network analysis, we found evidence that poor sleep quality, fatigue, CRP, and IL-6 were the most important variables in these complex interconnections. Our findings may assist future studies to disentangle the role of inflammation and psychoneurological symptoms in progression of HNC-related outcomes over time.

References

1. Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. Oncology. 2016;91(1):13-23.
2. Alho O-P, Teppo H, Mäntyselkä P, Kantola S. Head and neck cancer in primary care: presenting symptoms and the effect of delayed diagnosis of cancer cases. Cmaj. 2006;174(6):779-84.
3. Moore K, Ford P, Farah C. "I have quality of life… but…": exploring support needs important to quality of life in head and neck cancer. European Journal of Oncology Nursing. 2014;18(2):192-200.
4. Macfarlane TV, Wirth T, Ranasinghe S, Ah-See KW, Renny N, Hurman D. Head and neck cancer pain: systematic review of prevalence and associated factors. Journal of oral & maxillofacial research. 2012;3(1).
5. Santoso AM, Jansen F, Lissenberg-Witte BI, de Jong RJB, Langendijk JA, Leemans CR, et al. Poor sleep quality among newly diagnosed head and neck cancer patients: prevalence and associated factors. Supportive Care in Cancer. 2021;29(2):1035-45.
6. Haisfield-Wolfe ME, McGuire DB, Soeken K, Geiger-Brown J, De Forge BR, editors. Prevalence and correlates of depression among patients with head and neck cancer: a systematic review of implications for research. Oncology nursing forum; 2009.
7. Nautiyal V, Lal P, Verma M, Yadav R, Singh N, Kumar S. Evaluation of fatigue in head and neck cancer patients undergoing (intensity modulated radiation therapy) radiotherapy: a prospective study. Asian Journal of Oncology. 2015;1(1).
8. So WK, Law BM, Ng MS, He X, Chan DN, Chan CW, et al. Symptom clusters experienced by breast cancer patients at various treatment stages: A systematic review. Cancer Medicine. 2021;10(8):2531-65.
9. Tometich DB, Small BJ, Carroll JE, Zhai W, Luta G, Zhou X, et al. Pretreatment psychoneurological symptoms and their association with longitudinal cognitive function and quality of life in older breast cancer survivors. Journal of pain and symptom management. 2019;57(3):596-606.
10. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychological bulletin. 2004;130(3):355.
11. Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. The Journal of Clinical Endocrinology & Metabolism. 2005;90(5):3106-14.
12. Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. Psychoneuroendocrinology. 2017;83:25-41.
13. Knight EL, Jiang Y, Rodriguez-Stanley J, Almeida DM, Engeland CG, Zilioli S. Perceived stress is linked to heightened biomarkers of inflammation via diurnal cortisol in a national sample of adults. Brain, Behavior, and Immunity. 2021;93:206-13.
14. Solomon I, Voiculescu VM, Caruntu C, Lupu M, Popa A, Ilie MA, et al. Neuroendocrine factors and head and neck squamous cell carcinoma: An affair to remember. Disease Markers. 2018;2018.
15. Chang W-P, Lin C-C. Relationships of salivary cortisol and melatonin rhythms to sleep quality, emotion, and fatigue levels in patients with newly diagnosed lung cancer. European Journal of Oncology Nursing. 2017;29:79-84.
16. Clevenger L, Schrepf A, Christensen D, DeGeest K, Bender D, Ahmed A, et al. Sleep disturbance, cytokines, and fatigue in women with ovarian cancer. Brain, behavior, and immunity. 2012;26(7):1037-44.
17. Himbert C, Ose J, Lin T, Warby CA, Gigic B, Steindorf K, et al. Inflammation-and angiogenesis-related biomarkers are correlated with cancer-related fatigue in colorectal cancer patients: Results from the ColoCare Study. European journal of cancer care. 2019;28(4):e13055.

18. Miranda DO, Anatriello E, Azevedo LR, Cordeiro JF, Peria FM, Flória-Santos M, et al. Elevated serum levels of proinflammatory cytokines potentially correlate with depression and anxiety in colorectal cancer patients in different stages of the antitumor therapy. Cytokine. 2018;104:72-7.
19. Xiao C, Beitler JJ, Higgins KA, Conneely K, Dwivedi B, Felger J, et al. Fatigue is associated with inflammation in patients with head and neck cancer before and after intensity-modulated radiation therapy. Brain, behavior, and immunity. 2016;52:145-52.
20. Oliveira K, von Zeidler S, Lamas A, de Podestá J, Sena A, Souza E, et al. Relationship of inflammatory markers and pain in patients with head and neck cancer prior to anticancer therapy. Brazilian Journal of Medical and Biological Research. 2014;47(7):600-4.
21. Shimba A, Ikuta K. Immune-enhancing effects of glucocorticoids in response to day–night cycles and stress. International Immunology. 2020;32(11):703-8.
22. Mac Giollabhui N. Inflammation and depression: research designs to better understand the mechanistic relationships between depression, inflammation, cognitive dysfunction, and their shared risk factors. Brain, Behavior, & Immunity-Health. 2021;15:100278.
23. Contreras A, Nieto I, Valiente C, Espinosa R, Vazquez C. The study of psychopathology from the network analysis perspective: a systematic review. Psychotherapy and Psychosomatics. 2019;88(2):71-83.
24. Verdonck-de Leeuw I, Jansen F, Brakenhoff R, Langendijk J, Takes R, Terhaard C, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. BMC cancer. 2019;19(1):1-13.
25. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. Frontiers in immunology. 2018;9:586.
26. Kalaoja M, Corbin LJ, Tan VY, Ahola-Olli AV, Havulinna AS, Santalahti K, et al. The role of inflammatory cytokines as intermediates in the pathway from increased adiposity to disease. Obesity. 2021;29(2):428-37.
27. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213.
28. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. Journal of pain and symptom management. 2004;27(2):140-8.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica. 1983;67(6):361-70.
30. Vodermaier A, Linden W, Siu C. Screening for emotional distress in cancer patients: a systematic review of assessment instruments. Journal of the National Cancer Institute. 2009;101(21):1464-88.
31. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.
32. Fayers P, Aaronson NK, Bjordal K, Sullivan M. EORTC QLQ–C30 scoring manual: European Organisation for Research and Treatment of Cancer; 1995.
33. Smets E, Garssen B, Bonke Bd, De Haes J. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of psychosomatic research. 1995;39(3):315-25.
34. Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology. 2009;34(10):1423-36.
35. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal statistical society: series B (Methodological). 1995;57(1):289-300.

36. Peeters CF, Bilgrau AE, van Wieringen WN. rags2ridges: A One-Stop-Shop for Graphical Modeling of High-Dimensional Precision Matrices. arXiv preprint arXiv:201005619. 2020.
37. Van Wieringen WN, Peeters CF. Ridge estimation of inverse covariance matrices from high-dimensional data. Computational Statistics & Data Analysis. 2016;103:284-303.
38. Fruchterman TM, Reingold EM. Graph drawing by force-directed placement. Software: Practice and experience. 1991;21(11):1129-64.
39. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. Behavior Research Methods. 2018;50(1):195-212.
40. Newman ME, Girvan M. Finding and evaluating community structure in networks. Physical review E. 2004;69(2):026113.
41. Pace-Schott EF, Germain A, Milad MR. Effects of sleep on memory for conditioned fear and fear extinction. Psychological bulletin. 2015;141(4):835.
42. McQuestion M, Fitch M. Patients' experience of receiving radiation treatment for head and neck cancer: Before, during and after treatment. Canadian Oncology Nursing Journal. 2016;26(4):325.
43. Recine TS. Contributions of Fatigue, Pain, and Functional Limitation to Future Depression in Cancer Survivors. 2016.
44. Stepanski EJ, Walker MS, Schwartzberg LS, Blakely LJ, Ong JC, Houts AC. The relation of trouble sleeping, depressed mood, pain, and fatigue in patients with cancer. Journal of Clinical Sleep Medicine. 2009;5(2):132-6.
45. Choudhary MM, France TJ, Teknos TN, Kumar P. Interleukin-6 role in head and neck squamous cell carcinoma progression. World journal of otorhinolaryngology-head and neck surgery. 2016;2(2):90-7.
46. Kishimoto T. Interleukin-6: discovery of a pleiotropic cytokine. Arthritis research & therapy. 2006;8(2):1-6.
47. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its behavioral and metabolic correlates: from HPA axis to glucocorticoid receptor dysfunction. Annals of the New York Academy of Sciences. 2012;1261:55.
48. Multhoff G, Molls M, Radons J. Chronic inflammation in cancer development. Frontiers in immunology. 2012;2:98.
49. Xiao C, Eldridge RC, Beitler JJ, Higgins KA, Chico CE, Felger JC, et al. Association Among Glucocorticoid Receptor Sensitivity, Fatigue, and Inflammation in Patients With Head and Neck Cancer. Psychosomatic medicine. 2020;82(5):508-16.
50. Szabo YZ, Slavish DC. Measuring salivary markers of inflammation in health research: A review of methodological considerations and best practices. Psychoneuroendocrinology. 2020:105069.

Chapter VI

General Discussion

The main purpose of this thesis was to provide insight into sleep quality and disturbances in HNC patients. This thesis started with an introduction on the clinical features of HNC and the quality of life of HNC patients, the physiological aspects of sleep, sleep measurements, and existing insight on sleep disturbances in the general population and cancer patients. Several studies were undertaken to address research gaps in sleep disturbances among newly diagnosed HNC patients. First, all literature on the prevalence of different types of sleep disturbances at different phases of the HNC trajectory was systematically reviewed. Then, the prevalence and risk factors of poor sleep quality before HNC treatment was examined. Subsequently, the prevalence and risk factors of sleep quality trajectories from diagnosis up to 6 months after treatment was examined. Finally, a network analysis was performed to examine the associations between poor sleep quality, psychological distress, fatigue, oral pain and biological markers of stress and inflammation among HNC patients before treatment. This chapter contains a summary and discussion of the main findings of studies in this thesis. In addition, methodological considerations as well as clinical and research implications are discussed.

Summary and discussion of the findings

Defining and measuring sleep disturbances in HNC patients before, during and after treatment

Establishing the prevalence of sleep disturbances in HNC patients is important to inform healthcare professionals about the magnitude of this problem, as well as assist researchers to design further studies on sleep interventions for HNC patients. To this end, a systematic review and meta-analysis was conducted to synthesize prevalence of various kinds of sleep disturbances in various HNC treatment phases (chapter **2**). Twenty-nine studies were included in this systematic review. These studies used different definitions of sleep disturbances which can be categorized into three categories: (symptoms of) insomnia, sleep-related breathing disturbances, and hypersomnolence. The pooled prevalence rate before and after curative treatment was 29% and 40% for insomnia, 16% and 32% for hypersomnolence, and 66% and 51% for sleep-related breathing disturbances.

The prevalence rates of sleep disorders based on DSM diagnosis criteria were lower than the prevalence rates based on self-reported symptom questionnaires. For example, the pooled prevalence rate of insomnia before HNC treatment was 21% for the full blown DSM disorder and 30% for the self-report questionnaire. After HNC treatment, the prevalence rates were respectively 23% (DSM disorder) and 46% (self-report). This finding was expected since symptoms of sleep disturbances are more

common than diagnosis but they are still important because subthreshold symptoms might also lead to considerable patient burden. This finding is also a clear example of variation in prevalence rates of sleep disturbance due to measurement method of choice. Ohayon and Reynolds suggested that self-reported sleep disturbance is preferred when the population of interest is general population and/or general clinical practice, whereas diagnosis-based sleep disorder can be applied to evaluate effectiveness of an intervention for a specific sleep disorder[1]. This suggestion was based on findings from their multi-national study in over 25,000 adults from the general population, where a large proportion of participants reported sleep complaints, even though they did not fit into diagnosis criteria of insomnia disorder[1]. It is therefore important to clearly define the type of sleep disturbance of interest based on the specific research question or clinical endpoint and choose the sleep measurement instrument accordingly.

In chapter **3**, the sleep quality of HNC patients before treatment was further examined using baseline data of the NETherlands QUality of life and Biomedical Cohort (NET-QUBIC). In NET-QUBIC study, sleep quality was measured using PSQI which has good validity and reliability to measure important components of sleep quality and disturbances in cancer patients[2, 3]. The main finding of this study was that 44% of HNC patients had a poor sleep quality (PSQI total score > 5) before starting treatment. This prevalence is higher than that of the general population (36%)[4]. HNC symptoms and psychological distress due to recent diagnosis of cancer may contribute to this higher prevalence. In addition, 42% of HNC patients had poor sleep efficiency (the ratio of sleeping time and time spent in bed is < 85%) and 45% reported nighttime or early morning awakening at least three times a week (chapter 3). These prevalence rates are also higher than those of general population[1, 5]. This finding underlines the importance to screen for poor sleep quality in newly diagnosed HNC patients, especially sleep efficiency and nighttime/early morning awakening since these symptoms are two key symptoms of insomnia.

Chapter **4** showed that one out of five HNC patients had persistent poor sleep from treatment onset until 6 months after finishing treatment. Major life stress (e.g., cancer diagnosis and treatment) may impact sleep quality differently across individuals. Some people easily develop poor sleep quality after experiencing stressful life events while the others do not. Such vulnerability to develop poor sleep quality is also known as sleep reactivity[6]. Those with low sleep reactivity hardly experience poor sleep after stress exposure, while those with high sleep reactivity prone to suffer from poor sleep soon after stress exposure[6]. Newly diagnosed HNC patients in our study (chapter **4**) who persistently had good sleep quality (37.6%) until 6 months after treatment may represent low-reactive sleepers; the diagnosis and treatment of HNC seemed to minimally affect their sleep quality. On the other side, HNC patients who persistently

had poor sleep until 6 months after treatment (21.8%) may have high sleep reactivity and they may have high risk of having chronic insomnia disorder[7]. Hence, it is important to recognize this group of patients soon after HNC diagnosis and provide timely intervention. Meanwhile, 29% of HNC patients who had alternating or improving sleep quality may have experienced a transient poor sleep quality. These patients may be vulnerable to new episodes of poor sleep quality in the long run[7] and they may need periodic sleep evaluation throughout HNC survivorship. Recognizing personal and HNC-related characteristics of these high-risk individuals may be helpful to start sleep intervention timely.

The association between personal factors and pre-treatment symptoms and poor sleep quality in HNC patients

Female, younger age, passive coping style, worse pre-treatment oral pain, and worse pre-treatment sexual interest and enjoyment corresponded to greater odds of having poor sleep quality before HNC treatment (chapter **3**). Those who had a higher risk to have persistent poor sleep quality (instead of having persistent good sleep quality) were women, patients who used painkillers before treatment, and those who had more anxiety symptoms before treatment (chapter **4**).

Savard and Morin described three main factors involved in development and maintenance of insomnia in cancer patients: predisposing, precipitating, and perpetuating factors[8]. I will refer to these factors to reflect on the main findings in chapter **3** and **4**. First, predisposing factors are traits which may increase the general vulnerability of having poor sleep quality[8]. Based on our findings, being a woman, being diagnosed with HNC at a younger age, and having passive coping style seemed to be the predisposing factors of having poor sleep quality before starting HNC treatment. In addition, being a woman also seemed to be predisposing factor of having persistent poor sleep quality until 6 months after treatment. Biological factors, such as menopausal symptoms, are strongly associated with worse insomnia symptoms in midlife women[9] and this may explain worse sleep quality in women with HNC. Younger HNC patients experience worse psychological distress[10] and higher fear of cancer progression than older HNC patients[11], which may contribute to their higher risk of having poor sleep quality. HNC patients who had passive coping style, a form of emotion-focused coping, may focus on their negative emotions related to their cancer diagnosis, causing them to sleep poorly, as general population who use this maladaptive coping strategy in stressful condition also tend to have worse sleep quality[9].

Precipitating factors are stressful life events which initiate sleep disturbance or worsen a pre-existing sleep disturbance[8]. Being diagnosed with HNC is of course an example of

a very stressful life event and is therefore to be expected to trigger the onset of poor sleep quality. The findings in chapter **3** showed that oral pain and problems in sexual interest/enjoyment seemed to be the most important symptoms associated with poor sleep quality before HNC treatment. These symptoms may precipitate poor sleep quality in newly-diagnosed HNC patients. HNC patients with oral pain at night may have poor sleep, while a disturbed sleep may in turn lower their pain threshold, increasing their perception of pain[12]. HNC patients with problems in sexual interest and enjoyment may actually have underlying problems in intimate relationships and lower emotional satisfaction, which may affect their sleep quality[13].

Perpetuating factors are inefficient sleep-wake behavior and dysfunctional cognition processes that the patient develops in reaction to having poor sleep quality which adversely maintain or worsen their poor sleep[8]. HNC patients may try to compensate their poor sleep and relieve their fatigue by staying longer in bed, taking naps during the day, or using sleep medications while this habit may eventually disrupt their sleep-wake rhythm[8]. HNC patients may also feel anxious around bedtime anticipating they will not get enough sleep or perform sleep-interfering activities before bedtime as a way to wind down (e.g., performing exercise, watching television, scrolling on mobile phone), which adversely disrupt their sleep quality. Chapter **3** showed that 15% of HNC patients before treatment used sleep medication at least once in a week. In addition, HNC patients who used painkillers and those who had worse anxiety before cancer treatment had higher odds of having persistent poor sleep until 6 months after treatment (chapter **4**). Opioid painkillers are often prescribed in newly-diagnosed HNC patients[14] and may disrupt sleep-wake rhythm in the long term[15]. Future prospective study is needed to explore whether long-term anxiety and use of opioid painkillers and sleep medications contribute as perpetuating factors for persistent poor sleep in HNC patients.

All in all, the development of poor sleep quality in newly diagnosed HNC patients seem to be influenced by a broad range of factors: sociodemographic characteristics (sex, age), personal trait (coping style), behavior (use of pain medications), psychological symptoms (anxiety) as well as the multi-facetted psychobiological symptoms (pain and less sexual interest/enjoyment). Therefore, to understand the physiology of poor sleep quality in newly diagnosed HNC patients, one should evaluate it using a multifaceted approach, including sociodemographic, physical, psychological and biological parameters.

Psychoneurological symptoms, HPA-axis activity and inflammation in newly diagnosed HNC patients: an illustration of mind-body interrelationship

The complex relationship between mind and body has been discussed as early as 1641 by the French philosopher and mathematician, René Descartes[16]. In his essays, Descartes discussed whether and how the two seemingly opposites: mind and body, are related to each other[16]. In the 1990's, scientists began to look at the relationships between psychosocial stress, endocrine and immune system both in normal condition and in the presence of disease[17, 18]. Since the beginning of this century, there is a bourgeoning field of research which investigates the associations between psychoneurological symptoms (e.g., poor sleep, psychological distress, pain, fatigue), HPA-axis disruption, and inflammation in breast, lung, and mixed type cancer patients[19]. At the time of writing this thesis, several studies in newly diagnosed HNC patients showed significant associations between poor sleep quality, anxiety and higher catecholamine levels[20]; pain and higher inflammatory markers (i.e. CRP and TNF-α)[21]; and fatigue and higher inflammatory markers (i.e. IL-6 and CRP)[22].

In chapter **5**, network analysis was used to simultaneously evaluate the interconnections between worse psychoneurological symptoms (e.g., poor sleep, psychological distress, oral pain, fatigue), flatter cortisol slope, higher inflammation markers in HNC patients, older age, and higher BMI in HNC patients before treatment. Poor sleep quality, fatigue, CRP, and IL-6 were the most important variables in the interconnections between all variables. IL-6 was also the most important variable which connected two clusters found in the analysis: the psychoneurological symptoms – cortisol slope – CRP cluster with the cytokines – age – and BMI cluster. This finding suggests screening and treating multiple psychoneurological symptoms at once is perhaps more effective than focusing on a single symptom, since all psychoneurological symptoms are connected to each other. Although several studies have evaluated interventions which target multiple symptoms in patients with lung, breast and mixed-type of cancer[23], similar research in HNC patients is still lacking.

Methodological considerations

Strengths

There are several strengths of the studies contained in this thesis. First, to the best of our knowledge, our systematic review and meta-analysis was the first of its kind to synthesize the prevalence of insomnia, hypersomnolence, and sleep-related breathing disturbances in HNC patients across all treatment phases, as well as to critically assess the methodological quality of the available literature. Second, PSQI was used in chapter

3, 4, and 5 to measure sleep quality. PSQI is a valid and reliable instrument to measure sleep quality among general population and cancer patients[2, 4] and has the advantage of covering a broad range of domains relevant to self-report sleep quality[24]. Third, network analysis was used to illustrate the associations between symptoms (poor sleep quality, psychological symptoms, fatigue, and oral pain), HPA-axis activity, and inflammation markers in HNC patients. This integrative approach provides a systemic view on the complex interconnections instead of examining single associations, taking into account each association with all other variables of interest, and gives indication of which variables are relatively more important than the rest. Another strength is the use of data from a large multicenter cohort, the NET-QUBIC, which included 739 HNC patients generally representative of the Dutch HNC population, and captured extensive measures of sociodemographic, clinical, physical, psychological, social, lifestyle, and biological characteristics from before treatment until 5 years after treatment[25].

Limitations

There are also some limitations of the studies in this thesis. First, no objective parameters of sleep were measured, either by polysomnography, actigraphy, or multiple sleep latency test. Thus, no data is available on the architecture of sleep, the frequency and severity of abnormal breathing during sleep, or periodic measure of the sleep-wake cycles. While such objective measures are the golden standard for specific sleep disorders such as obstructive sleep apnea and central disorders of hypersomnolence, these measurements are time-consuming and labor-intensive. In regard to the NET-QUBIC study, where an extensive list of measurements was performed throughout multiple time-points, the use of the (validated) sleep questionnaire rather than objective sleep measure is a compromise between the feasibility of data collection from a large sample and an accurate objective information on sleep disorder parameters.

Second, it is unknown whether HNC patients already had sleep disturbances prior to receiving HNC diagnosis, so it is unclear whether poor sleep quality before HNC treatment is a reaction to the cancer diagnosis itself or rather a continuation or aggravation of pre-existing sleep disturbances. This limitation (or rather a challenge) is applicable to all studies examining sleep disturbances in cancer patients[8]. One way to record the history of sleep disturbances prior to HNC diagnosis is by asking the respondents retrospectively, but this approach is prone to recall bias. Another way is to record sleep disturbance prospectively in a general population who has increased risk for HNC, but this approach clearly needs a much larger sample size and an extensive follow-up period.

Recommendations

Clinical implications

A systematic review of clinical guidelines in detection and management of sleep disturbances in cancer patients concluded that most guidelines suggested a two-step assessment of sleep disturbance in cancer patients: first assessment is intended to be an initial screening as well as to rule out comorbidity; the second assessment includes more elaborated measures such as a 2-week sleep diary, beliefs and behaviors about sleep, as well as detailed history taking, physical examination and drug history[26]. In the Netherlands, a specific guideline for detection and management of sleep disturbances in cancer patients is only available for palliative care patients and a revision of its current version (published in 2008) is due in 2023[27]. A more general guideline "Detection of psychosocial care needs" (published in Dutch) recommended to use an instrument which covers a broad range of psychosocial wellbeing and quality of life (QOL) domains in adults with cancer, but there is no specific recommendation that sleep disturbances is mandatory to be measured[28]. This guideline mentioned three questionnaires in their recommendation[28] and each has one item on global sleep disturbance[29-31]. An advantage of using these questionnaires is the possibility to simultaneously detect and treat co-morbid symptoms which are associated with poor sleep quality, as found in chapter **2, 3 and 4** in this thesis, e.g. pain, anxiety, depression, fatigue and problems with sexual interest/enjoyment. The drawback is the inability to measure various domains of sleep disturbance. A possible solution for this issue is using computerized adapted testing (CAT), for example the CAT version of European Organization of Research and Treatment of Cancer measure of insomnia (EORTC CAT-SL)[32]. Using the CAT approach, more specific questions on different domains of sleep disturbances can be added to the questionnaire one at a time, depends on the outcome of preceding questions. This enables researchers and clinicians to get more information without burdening the patients with too much questionnaire items.

The Dutch guideline for psychosocial care in cancer patients [28] recommended that the first screening for psychosocial distress should be performed between first and second hospital visit (shortly after receiving diagnosis of HNC, before starting HNC treatment, and preferably not in the same consult as the diagnosis). When necessary, a thorough sleep assessment can be performed e.g. (medication) history taking, sleep diary, a specific questionnaire for sleep disturbance, or objective sleep assessment. Findings from studies in chapter **2**, **3**, and **4** underline the importance of periodic follow-up sleep assessments, alone or as a part of QOL measures, especially in patients with high risk of having persistent poor sleep quality. The follow-up assessments can be performed either by medical specialists, oncological nurses, general practitioners, or medical psychologists. Furthermore, the Dutch guideline recommended that follow-up

assessment of psychosocial care needs in-between cancer treatment to be performed maximum once per 3 months, especially at time-points when patients often have worse symptoms and distress[28]. These critical time-points for follow-up assessments are the beginning or the end of treatment, during transitions between curative to palliative intent, and when HNC recurrence or metastasis is detected[28, 33, 34].

It is important to take into account that newly diagnosed HNC patients often need some time to adjust to the stress induced by receiving cancer diagnosis[33, 34]. A digital questionnaire may be preferable, as it enables healthcare practitioners to integrate reminders to fill in the form so that patients can fill it in at the convenient time and place. In addition, a digital (web-based) questionnaire enables healthcare practitioner to directly access the filled-in form and decide a suitable treatment. An example of this digital questionnaire is OncoQuest, an online patient-reported outcome measure which is routinely administered in outpatient oncological care in Amsterdam University Medical Center, location VUMC, the Netherlands[35].

Together with the patients, practical issues of the sleep intervention should be discussed, e.g., whether professional support would be needed or a self-management is already sufficient. A recent Dutch study on a web-based self-management application Oncokompas for HNC and other cancer survivors found sleep disturbance as the second most chosen symptom they would like to address, after fatigue[36]. Also, more information is needed whether sleep intervention is feasible to be initiated before starting cancer treatment. It is inevitable that, as there was limited research on the epidemiology of sleep disturbances in newly diagnosed HNC patients, there is also limited research on the effectiveness of sleep interventions in HNC patients. We will discuss this issue in the Scientific implications section below.

Scientific implications

In chapter **2** we found that most of the studies had inadequate methodological quality due to inadequate sample size, lack of information about participant recruitment, and use of non-validated instruments to measure sleep disturbances. Future studies on sleep disturbances in HNC patients should avoid these methodological pitfalls by including a sufficient sample size, identify and report the clinical parameters of included versus excluded patients, and use a validated instrument to measure the type of sleep disturbance of interest.

Our cross-sectional approach in chapter **5** did not allow us to investigate the causality and associations over-time between poor sleep quality, psychological distress, fatigue, oral pain, HPA-axis activity, and inflammatory biomarkers. For example, in chapter **5** there was a direct connection between poor sleep quality and worse cortisol diurnal

rhythm, as well as an indirect connection between poor sleep quality and higher inflammation (via pain or fatigue). A prospective study is needed to examine whether HNC patients with persistent poor sleep are at risk of worse HPA-axis activity and inflammatory disruption in the longer term, as well as of worse clinical outcomes such as HNC progression, recurrence, and survival. Also, network analysis in chapter **5** showed that poor sleep quality and fatigue had the most central position. More research is needed to confirm whether these symptoms are "common-cause" or rather "common-effect" symptoms.

Furthermore, more (and better) research is needed to develop and evaluate intervention for poor sleep quality in newly-diagnosed HNC patients, emphasizing on intervention which can alleviate multiple symptoms at once. A systematic review and meta-analysis on psychological intervention studies in HNC patients analyzed 5 studies on cognitive behavioral therapy (CBT) and one study on mindfulness-based stress reduction[37]. However, no firm conclusion can be drawn on the efficacy of these interventions due to inadequate study quality, especially due to too small sample sizes, no randomization, and no control group[37]. Also, none of the studies included sleep quality in their outcome measures[37]. Well-designed randomized controlled trials on sleep interventions in newly-diagnosed HNC patients are therefore needed. It can be useful to develop a guided web-based CBT tailored to newly-diagnosed HNC patients, as a comparable intervention is demonstrated to be feasible and effective to improve sleep quality in breast cancer patients[38].

Main conclusion

Newly diagnosed HNC patients often experience poor sleep quality and a significant part of these patients continues to have poor sleep until 6 months after finishing treatment. Early and periodic screening of sleep problems as part of QOL monitoring is recommended throughout all HNC treatment phases to identify those patients who may need to be referred to sleep interventions. More research is needed into the pathology of poor sleep in HNC patients in the longer term, especially in relation with other psychoneurological symptoms and HPA-axis activity and inflammation.

References

1. Ohayon MM, Reynolds III CF. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep medicine. 2009;10(9):952-60.
2. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. Journal of pain and symptom management. 2004;27(2):140-8.
3. Akman T, Yavuzsen T, Sevgen Z, Ellidokuz H, Yilmaz AU. Evaluation of sleep disorders in cancer patients based on Pittsburgh Sleep Quality Index. European journal of cancer care. 2015;24(4):553-9.
4. Hinz A, Glaesmer H, Brähler E, Löffler M, Engel C, Enzenbach C, et al. Sleep quality in the general population: psychometric properties of the Pittsburgh Sleep Quality Index, derived from a German community sample of 9284 people. Sleep medicine. 2017;30:57-63.
5. Desjardins S, Lapierre S, Hudon C, Desgagné A. Factors involved in sleep efficiency: a population-based study of community-dwelling elderly persons. Sleep. 2019;42(5):zsz038.
6. Drake CL, Pillai V, Roth T. Stress and sleep reactivity: a prospective investigation of the stress-diathesis model of insomnia. Sleep. 2014;37(8):1295-304.
7. Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, Tran KM, Anderson JR, Roth T, et al. Hyperarousal and sleep reactivity in insomnia: current insights. Nature and science of sleep. 2018:193-201.
8. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. Journal of clinical oncology. 2001;19(3):895-908.
9. Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. Psychosomatic medicine. 2003;65(2):259-67.
10. Krok JL, Baker TA, McMillan SC. Age differences in the presence of pain and psychological distress in younger and older cancer patients. Journal of Hospice & Palliative Nursing. 2013;15(2):107-13.
11. Mirosevic S, Thewes B, van Herpen C, Kaanders J, Merkx T, Humphris G, et al. Prevalence and clinical and psychological correlates of high fear of cancer recurrence in patients newly diagnosed with head and neck cancer. Head & Neck. 2019;41(9):3187-200.
12. Wei Y, Blanken TF, Van Someren EJ. Insomnia really hurts: Effect of a bad night's sleep on pain increases with insomnia severity. Frontiers in Psychiatry. 2018;9:377.
13. Sprajcer M, O'Mullan C, Reynolds A, Paterson JL, Bachmann A, Lastella M. Sleeping together: Understanding the association between relationship type, sexual activity, and sleep. Sleep Science. 2022;15(Spec 1):80.
14. Henry M, Alias A, Frenkiel S, Richardson K, Hier M, Zeitouni A, et al. Contribution of psychiatric diagnoses to extent of opioid prescription in the first year post-head and neck cancer diagnosis: A longitudinal study. Psycho-Oncology. 2019;28(1):107-15.
15. Van Gastel A. Drug-induced insomnia and excessive sleepiness. Sleep medicine clinics. 2018;13(2):147-59.
16. Westphal J. The mind-body problem: MIT Press; 2016.
17. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. Thorax. 1998;53(12):1066-74.
18. Ader R, Cohen N. Psychoneuroimmunology: interactions between the nervous system and the immune system. The Lancet. 1995;345(8942):99-103.
19. Kim H-J, Barsevick AM, Fang CY, Miaskowski C. Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer nursing. 2012;35(6):E1-E20.
20. Bastos DB, Sarafim-Silva BA, Sundefeld MLM, Ribeiro AA, Brandão JD, Biasoli ÉR, et al. Circulating catecholamines are associated with biobehavioral factors and anxiety symptoms in head and neck cancer patients. PLoS One. 2018;13(8):e0202515.

21. Oliveira K, von Zeidler S, Lamas A, de Podestá J, Sena A, Souza E, et al. Relationship of inflammatory markers and pain in patients with head and neck cancer prior to anticancer therapy. Brazilian Journal of Medical and Biological Research. 2014;47:600-4.
22. Xiao C, Beitler JJ, Higgins KA, Conneely K, Dwivedi B, Felger J, et al. Fatigue is associated with inflammation in patients with head and neck cancer before and after intensity-modulated radiation therapy. Brain, behavior, and immunity. 2016;52:145-52.
23. Kwekkeboom KL, Wieben A, Stevens J, Tostrud L, Montgomery K, editors. Guideline-Recommended Symptom Management Strategies That Cross Over Two or More Cancer Symptoms. Oncology Nursing Forum; 2020.
24. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. Sleep medicine reviews. 2016;25:52-73.
25. Verdonck-de Leeuw I, Jansen F, Brakenhoff R, Langendijk J, Takes R, Terhaard C, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. BMC cancer. 2019;19(1):1-13.
26. Howell D, Oliver T, Keller-Olaman S, Davidson J, Garland S, Samuels C, et al. Sleep disturbance in adults with cancer: a systematic review of evidence for best practices in assessment and management for clinical practice. Annals of Oncology. 2014;25(4):791-800.
27. IKNL. Ontwikkeling richtlijnen: Integraal Kankercentrum Nederland; 2021 [Available from: https://iknl.nl/palliatieve-zorg/richtlijnen/ontwikkeling-richtlijnen.
28. Detecteren behoefte psychosociale zorg [Internet]. Kennisinstituut van de Federatie van Medisch Specialisten Nederlandse Vereniging voor Psychosociale Oncologie. 2017 [cited 16 June 2022]. Available from: https://richtlijnendatabase.nl/richtlijn/detecteren_behoefte_psychosociale_zorg/algemeen.html.
29. Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. Journal of clinical oncology. 2007;25(29):4670-81.
30. Braeken AP, Kempen GI, Watson M, Houben RM, Gils FCv, Lechner L. Psychometric properties of the Dutch version of the Mental Adjustment to Cancer scale in Dutch cancer patients. Psycho-Oncology. 2010;19(7):742-9.
31. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.
32. Dirven L, Petersen MA, Aaronson NK, Chie W-C, Conroy T, Costantini A, et al. Development and Psychometric Evaluation of an Item Bank for Computerized Adaptive Testing of the EORTC Insomnia Dimension in Cancer Patients (EORTC CAT-SL). Applied Research in Quality of Life. 2021;16:827-44.
33. Pirl WF, Fann JR, Greer JA, Braun I, Deshields T, Fulcher C, et al. Recommendations for the implementation of distress screening programs in cancer centers: report from the American Psychosocial Oncology Society (APOS), Association of Oncology Social Work (AOSW), and Oncology Nursing Society (ONS) joint task force. Cancer. 2014;120(19):2946-54.
34. Williams C. Psychosocial distress and distress screening in multidisciplinary head and neck cancer treatment. Otolaryngologic Clinics of North America. 2017;50(4):807-23.
35. Duman-Lubberding S, van Uden-Kraan C, Jansen F, Witte B, Eerenstein SE, Van Weert S, et al. Durable usage of patient-reported outcome measures in clinical practice to monitor health-related quality of life in head and neck cancer patients. Supportive Care in Cancer. 2017;25:3775-83.
36. van der Hout A, van Uden-Kraan C, Holtmaat K, Jansen F, Lissenberg-Witte BI, Nieuwenhuijzen GA, et al. Reasons for not reaching or using web-based self-management applications, and the use and

evaluation of Oncokompas among cancer survivors, in the context of a randomised controlled trial. Internet Interventions. 2021;25:100429.

37. Calver L, Tickle A, Moghaddam N, Biswas S. The effect of psychological interventions on quality of life in patients with head and neck cancer: A systematic review and meta-analysis. European journal of cancer care. 2018;27(1):e12789.

38. Dozeman E, Verdonck-de Leeuw IM, Savard J, van Straten A. Guided web-based intervention for insomnia targeting breast cancer patients: feasibility and effect. Internet interventions. 2017;9:1-6.

Appendices

Summary

Sleep quality is essential for optimal health and wellbeing of each individual. Previous research hypothesized that a good night's sleep plays important role not only in energy conservation and emotional regulation, but also in maintaining diurnal rhythm of hypothalamic-pituitary-adrenal (HPA) axis. Sleep disturbances, together with physical and psychological distress, are known to disrupt HPA-axis activity, causing changes in normal fluctuation of cortisol level. This may further affect physiological functions of cortisol, among which the most important is regulation of inflammatory response.

Despite extensive research on sleep quality in cancer patients in general, similar research in head and neck cancer (HNC) patients is scarce. HNC patients often suffer from psychological distress and physical symptoms starting from cancer diagnosis throughout treatment completion. These symptoms often compromise their quality of life and may play a role in their sleep quality. However, the prevalence of different kind of sleep disturbances in HNC patients throughout different treatment phases is unclear. We did not know which group of HNC patients already have poor sleep quality before the start of cancer treatment. We also did not know how sleep quality of HNC patients evolves overtime, and which HNC patients tend to have persistent poor sleep quality. Last but not least, there is lack of research which highlights the complex relationship between sleep quality, pain, fatigue, psychological distress, HPA-axis, and inflammation in newly diagnosed HNC patients. This thesis aims to address these research gaps by investigating the epidemiology, trajectories, and associated factors of poor sleep quality in newly diagnosed HNC patients, taking into account personal, physical, psychological, and biological parameters.

Chapter 2 investigated the prevalence rates of various types of sleep disturbances among HNC patients before, during, and after cancer treatment. PubMed, Embase, CINAHL, and PsycINFO were systematically searched to find studies that reported the prevalence of any type of sleep disturbance among adult HNC patients. Twenty nine studies of accumulatively 2,315 HNC patients were included. The quality of the studies was fairly low and the heterogeneity was high. These studies examined three types of sleep disturbances: insomnia, hypersomnolence, and sleep-related breathing disturbances. The pooled prevalence of insomnia was 29% (95% CI 20 – 41%) before treatment, 45% (95%CI 33 – 58%) during treatment, and 40% (95%CI 24 – 58%) after treatment, while for hypersomnolence the prevalence was 16% (95% CI 7 – 32%) before treatment and 32% (95% CI 20 – 48%) after treatment. The prevalence of sleep-related breathing disturbances before and after treatment was 66% (95% CI 44 – 82%) and 51% (95% CI 34 – 67%), respectively. These results imply that sleep disturbances are highly prevalent among HNC patients before, during, and after treatment. To

confirm these findings, however, we need more good quality studies with sufficient sample sizes and validated sleep measures.

Chapter 3 examined the prevalence and the associated factors of poor sleep quality in HNC patients before starting treatment. Pittsburgh Sleep Quality Index (PSQI) was used to measure the extent of sleep quality and disturbances in newly diagnosed HNC patients. Poor sleep quality was defined as a PSQI total score of > 5. Among 560 HNC patients included in the analysis, 246 (44%) had poor sleep quality before start of treatment. Younger age (odds ratio [OR] for each additional year 0.98, 95% CI 0.96 – 1.00), being female (OR 2.6, 95% CI 1.7 – 4.1), higher passive coping style (OR 1.18, 95% CI 1.09 – 1.28), more oral pain (OR 1.10, 95% CI 1.01 – 1.19), and less sexual interest and enjoyment (OR 1.13, 95% CI 1.06 – 1.20) were found to be significantly associated with poor sleep. These results imply that poor sleep quality is highly prevalent among HNC patients before start of treatment. Information about age, gender, coping style, as well as the extent of oral pain and sexual problems may aid clinicians to identify newly diagnosed HNC patients who may benefit from early sleep assessment and intervention.

Chapter 4 described the trajectories of sleep quality shortly after HNC diagnosis up to 6-month after treatment, as well as the pre-treatment risk factors for less favourable sleep trajectories. Poor sleep quality was defined as PSQI total score of > 5. Among 412 HNC patients, 37.6% had persistent good, 21.8% had persistent poor, 16.5% had improving, 10.9% had worsening, and 13.1% had alternating sleep quality trajectory. Compared to persistent good sleepers, persistent poor sleepers were more likely to be woman (OR=1.98, 95% CI 1.01 – 3.90), use painkillers prior to treatment (OR=2.52, 95% CI 1.33 – 4.77), and have worse pre-treatment anxiety symptoms (OR=1.26, 95% CI 1.15 – 1.38). These results demonstrated that unfavourable sleep quality trajectories are prevalent among HNC patients from pre-treatment to 6-month after treatment. A periodic sleep evaluation starting shortly after HNC diagnosis is necessary to identify persistent sleep problems, especially among high-risk group.

Chapter 5 explored the relationships between psychoneurological symptoms (poor sleep quality, anxiety, depression, fatigue, and pain), cortisol diurnal rhythm as indicator of HPA-axis activity, and inflammation markers (i.e., C-reactive protein [CRP], tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, IL-6 and IL-10) in 264 newly diagnosed HNC patients, taking into account relevant covariates (age and body mass index [BMI]). Network analysis was used to visualize these complex relationships. Three indices were calculated to determine the most central variable in the network. Poor sleep quality and fatigue had the highest degree index (i.e., both had the highest number of connections with other variables), fatigue and CRP had the highest closeness index (both had the closest proximity to all other variables), and IL-6 had the highest betweenness index (it was most often located on the shortest path between any pair of

other variables). The network model yielded two clusters: a symptoms – cortisol slope – CRP cluster and a IL-6 – IL-10 – TNF-α – age – BMI cluster. Both clusters were connected most prominently via IL-6. These findings provide evidence that poor sleep quality, fatigue, CRP, and IL-6 play an important role in the interconnections between psychoneurological symptoms and biomarkers of stress and inflammation in newly diagnosed HNC patients.

In summary, findings in this thesis suggest that screening for poor sleep quality in HNC patients should be started shortly after HNC diagnosis. Moreover, it is important to first clearly define the type of sleep disturbance of interest and then choose a validated sleep screening instrument accordingly. A periodic sleep evaluation should be aimed to HNC patients who are more at risk of having persistent poor sleep quality. This group of patients may benefit from early intervention which simultaneously targets poor sleep quality and other (psychoneurological) symptoms. These findings also provide directions for future research, for example into the long-term effects of poor sleep quality, disruptions of HPA-axis and inflammatory dysregulations on HNC progression and survival.

Samenvatting

Een goede slaap is essentieel voor optimale gezondheid en welzijn. Eerder onderzoek veronderstelde dat een goede nachtrust niet alleen een belangrijke rol speelt bij het behoud van energie en de regulatie van emotie, maar ook bij het handhaven van het diurnale ritme van de hypothalamus-hypofyse-bijnier (in het Engels afgekort als HPA) as. Eerder onderzoek heeft aangetoond dat slaapproblemen, samen met fysieke klachten en psychologische distress, de activiteit van de HPA-as kunnen verstoren en de fluctuatie van het cortisolniveau kunnen beïnvloeden. Dit kan de fysiologische functies van cortisol verder verstoren, waarvan een van de belangrijkste de regulatie van het immuunsysteem is.

Er is reeds veelvoudig onderzoek verricht naar slaapproblemen bij kankerpatiënten in het algemeen. Er is echter nog onvoldoende duidelijk over slaapproblemen bij hoofd-halskankerpatiënten. Patiënten met hoofd-halskanker krijgen vaak te maken met fysieke en psychische klachten al vanaf het moment van diagnose tot na de behandeling. Deze klachten hebben aanzienlijk effect op de kwaliteit van leven voor deze patiëntengroep en mogelijk ook op hun slaapkwaliteit. De prevalentie van verschillende soorten slaapproblemen bij hoofd-halskankerpatiënten in verschillende behandelingsfasen is echter onduidelijk. Het is nog niet duidelijk welke hoofd-halskankerpatiënten al slaapproblemen hebben vóór de start van de kankerbehandeling. Hoe de slaapkwaliteit van hoofd-halskankerpatiënten in de loop van de tijd evolueert en welke groep patiënten aanhoudende slaapproblemen hebben zijn evenmin duidelijk. Tevens is er meer kennis nodig rond de complexe relatie tussen slaapproblemen, pijn, vermoeidheid, psychologische distress, HPA-as, en immuunsysteem bij nieuw gediagnosticeerde hoofd-halskankerpatiënten. Dit proefschrift heeft als doel deze kennishiaten aan te pakken door onderzoek naar de epidemiologie, beloop en geassocieerde factoren van slaapproblemen bij hoofd-halskankerpatiënten, rekening houdend met persoonlijke, fysieke, psychologische en biologische eigenschappen.

Hoofdstuk 2 beschrijft de prevalentie van verschillende soorten slaapproblemen bij hoofd-halskankerpatiënten zowel voor, tijdens als na kankerbehandeling. PubMed, Embase, CINAHL en PsycINFO werden systematisch doorzocht om studies te vinden die de prevalentie van slaapproblemen bij hoofd-halskankerpatiënten hebben gerapporteerd. Negenentwintig studies met in totaal 2.315 hoofd-halskankerpatiënten werden geïncludeerd. De kwaliteit van de studies was matig en de heterogeniteit was hoog. Deze onderzoeken onderzochten drie soorten slaapproblemen: insomnie, hypersomnie en slaapgerelateerde ademhalingsstoornissen. De gepoolde prevalentie van insomnie was 29% (95% CI 20 – 41%) vóór de behandeling, 45% (95% CI 33 – 58%) tijdens de behandeling en 40% (95% CI 24 – 58%) na de behandeling. Voor

hypersomnie was de prevalentie 16% (95% CI 7 – 32%) vóór de behandeling en 32% (95% CI 20 – 48%) na de behandeling. De prevalentie van slaapgerelateerde ademhalingsstoornissen voor en na de behandeling was respectievelijk 66% (95% CI 44 – 82%) en 51% (95% CI 34 – 67%). Deze bevindingen suggereren dat slaapproblemen veel voorkomen bij hoofd-halskankerpatiënten zowel vóór, tijdens als na de behandeling. Om deze bevindingen verder te bevestigen, zijn meer kwalitatief hoogstaande studies nodig met voldoende steekproefgrootte en gebruik van een gevalideerd slaapmeetinstrument.

In **hoofdstuk 3** werd de prevalentie van slechte slaap en factoren die hiermee associëren onderzocht bij hoofd-halskankerpatiënten voordat ze met kankerbehandeling zijn begonnen. Pittsburgh Sleep Quality Index (PSQI) werd gebruikt om de mate van slaapkwaliteit en -problemen te meten. Slechte slaap werd gedefinieerd als een PSQI-totaalscore van > 5. Van de 560 hoofd-halskankerpatiënten die in de analyse werden geïncludeerd, hadden 246 (44%) een slechte slaap vóór de behandeling. Jongere leeftijd (odds ratio [OR] voor elk extra leeftijdsjaar 0,98; 95% CI 0,96 – 1,00), vrouw zijn (OR 2,6; 95% CI 1,7 – 4,1), meer passieve copingstrategie (OR 1,18; 95% CI 1,09 – 1,28), meer pijn (OR 1,10; 95% CI 1,01 – 1,19) en minder seksuele interesse en seksueel plezier (OR 1,13, 95% CI 1,06 – 1,20) bleken significant geassocieerd te zijn met slechte slaap. Deze resultaten suggereren dat slechte slaap veel voorkomt bij hoofd-halskankerpatiënten vóór de behandeling. Informatie over leeftijd, geslacht, copingstrategie, evenals de mate van pijn en seksuele problemen kunnen zorgverleners ondersteunen om nieuw gediagnosticeerde hoofd-halskankerpatiënten te identificeren die kunnen profiteren van tijdige signalering van - en interventie voor - slaapproblemen.

Hoofdstuk 4 beschrijft het verloop van slaapkwaliteit kort na de diagnose van hoofd-halskanker tot 6 maanden na de behandeling, evenals factoren die geassocieerd zijn met een ongunstig verloop van slaapkwaliteit. Slechte slaap werd gedefinieerd als een PSQI-totaalscore van > 5. Van de 412 hoofd-halskankerpatiënten had 37,6% aanhoudend goed, 21,8% aanhoudend slecht, 16,5% verbeterde, 10,9% verslechterde en 13,1% had wisselend verloop van slaapkwaliteit. Vergeleken met patiënten met aanhoudend goede slaap, waren patiënten met aanhoudend slechte slaap vaker vrouw (OR=1,98, 95% CI 1,01 – 3,90). Ze gebruikten vóór de behandeling vaker pijnstillers (OR=2,52, 95% CI 1,33 – 4,77) en hadden vóór de behandeling ernstigere angstklachten (OR=1,26, 95% CI 1,15 – 1,38). Deze resultaten suggereren dat een ongustig verloop van slaapkwaliteit veel voorkomt bij hoofd-halskankerpatiënten vanaf het moment van diagnose tot 6 maanden na behandeling. Een reguliere slaapevaluatie vanaf de diagnose van hoofd-halskanker is nodig om aanhoudende slaapproblemen te identificeren, vooral bij risicogroepen.

In **hoofdstuk 5** werden de associaties tussen 'psychoneurologische' klachten (slechte slaap, angst, depressie, vermoeidheid en pijn), het diurnale ritme van cortisol (als indicator van HPA-as) en ontstekingsmarkers (*C-reactive protein* [CRP], *tumor necrosis factor alpha* [TNF-α], *interleukin* [IL]-6 and IL-10] bij 264 nieuw gediagnosticeerde hoofd-halskankerpatiënten onderzocht, rekening houdend met relevante covariabelen (leeftijd en Body Mass Index [BMI]). Netwerkanalyse werd gebruikt om deze complexe relaties te visualiseren. De meest centrale variabelen in het netwerk werden berekend in drie indicatoren. Slechte slaap en vermoeidheid hadden de hoogste 'degree' (d.w.z. beide hadden het hoogste aantal verbindingen met andere variabelen), vermoeidheid en CRP hadden de hoogste 'closeness' (beiden staan het dichtst bij alle andere variabelen) en IL-6 had de hoogste 'betweenness' (deze bevond zich meestal op het kortste pad tussen alle paren van andere variabelen). Het netwerkmodel leverde twee clusters op: symptomen – cortisol – CRP cluster en IL-6 – IL-10 – TNF-α – leeftijd – BMI cluster. Beide clusters waren het sterkst verbonden via IL-6. Deze bevindingen suggereren dat slechte slaap, vermoeidheid, CRP en IL-6 een belangrijke rol spelen in de complexe verbanden tussen psychoneurologische klachten en biomarkers van stress en ontsteking bij nieuw gediagnosticeerde hoofd-halskankerpatiënten.

Samenvattend, de bevindingen in dit proefschrift benadrukken het belang van tijdige signalering van slechte slaap bij nieuw-gediagnosticeerde hoofd-halskankerpatiënten. Het is belangrijk om eerst een duidelijke definitie te stellen om welk type slaapstoornis het gaat en vervolgens een gevalideerd slaapmeetinstrument te kiezen. Een reguliere slaapmeting moet op zijn minst worden toegepast bij patiënten die meer risico lopen op een aanhoudende slechte slaap. Deze groep patiënten kan baat hebben bij vroegtijdige interventie die gericht is op zowel slaapproblemen als andere (psychoneurologische) symptomen. Onze bevindingen geven ook aanwijzingen voor toekomstig onderzoek, bijvoorbeeld naar de langetermijneffecten van een slechte slaap, verstoringen van de HPA-as en ontregelingen van het immuunsysteem op de progressie en overleving van hoofdhalskanker.

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Non scholae, sed vitae discimus.

About the author

Angelina Maria Mirna Santoso was born and grew up surrounded by scenic mountains of Mt. Kawi, Mt. Arjuno and Mt. Semeru, among many others (Malang, Indonesia). During her general medicine training in Airlangga University (Surabaya, Indonesia), she deeply enjoyed exhanging thoughts and ideas with fellow medical students from abroad, which motivated her active participation in Asian Medical Students' Association and its international conferences. Her clinical internship during summer 2014 at department of Rehabilitation Medicine, University Medical Center Groningen has brought her interest to first pursue scientific training before continuing clinical specialization in medicine. Upon receiving her medical degree, she was granted Orange Tulip Scholarship to join research master programme in Radboud University (Nijmegen, the Netherlands), majoring in Human Pathobiology and Health Technology Assessment. After obtaining her diploma Master of Science in Biomedical Sciences she worked as a research assistant for the NILVAD study in department of Geriatrics, Radboudumc (Nijmegen, the Netherlands). Her research interest in health-related quality of life and patient-reported outcome measures (PROM) has provoked her to pursue a PhD with the department of Clinical, Neuro-, and Developmental Psychology, Vrije Universiteit (Amsterdam, the Netherlands). At the moment, she is finishing her clinical internship as a requirement to register her medical license in the Netherlands.

List of publications

Publications in this thesis

Santoso AM, Jansen F, Peeters CF, Baatenburg de Jong RJ, Brakenhoff RH, Langendijk JA, Leemans CR, Takes RP, Terhaard CH, van Straten A, Verdonck-de Leeuw IM. Psychoneurological Symptoms and Biomarkers of Stress and Inflammation in Newly Diagnosed Head and Neck Cancer Patients: A Network Analysis. Current Oncology. 2022 Sep 28;29(10):7109-21.

Santoso AM, Jansen F, Lissenberg-Witte BI, Baatenburg de Jong RJ, Langendijk JA, Leemans CR, Smit JH, Takes RP, Terhaard CH, van Straten A, Verdonck-de Leeuw IM. Sleep quality trajectories from head and neck cancer diagnosis to six months after treatment. Oral Oncology. 2021 Apr 1;115:105211.

Santoso AM, Jansen F, Lissenberg-Witte BI, Baatenburg de Jong RJ, Langendijk JA, Leemans CR, Smit JH, Takes RP, Terhaard CH, van Straten A, Verdonck-de Leeuw IM. Poor sleep quality among newly diagnosed head and neck cancer patients: prevalence and associated factors. Supportive Care in Cancer. 2021 Feb;29:1035-45.

Santoso AM, Jansen F, de Vries R, Leemans CR, van Straten A, Verdonck-de Leeuw IM. Prevalence of sleep disturbances among head and neck cancer patients: a systematic review and meta-analysis. Sleep medicine reviews. 2019 Oct 1;47:62-73.

Other publications

De Heus RA, Donders R, **Santoso AM**, Olde Rikkert MG, Lawlor BA, Claassen JA, Nilvad Study Group, Segurado R, Howard R, Pasquier F, Börjesson-Hanson A. Blood Pressure Lowering With Nilvadipine in Patients With Mild-to-Moderate Alzheimer Disease Does Not Increase the Prevalence of Orthostatic Hypotension. Journal of the American Heart Association. 2019 May 21;8(10):e011938.

Santoso AM, Lutomski JE, Hofman CS, Metzelthin SF, Blom JW, van der Wees PJ, Rikkert MG, Melis RJ, TOPICS-MDS Consortium. Development of a patient-reported outcome measure for geriatric care: the Older Persons and Informal Caregivers Survey Short Form. Value in Health. 2018 Oct 1;21(10):1198-204.

Lutomski JE, **Santoso AM**, Hofman CS, Rikkert MG, Melis RJ. Responsiveness of the full-length and short form of the older persons and informal caregivers survey. Journal of the American Medical Directors Association. 2017 Sep 1;18(9):804-5.