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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] 1.01–3.90), use painkillers prior to treatment (OR = 2.52, 95% CI 1.33–4.77), and have more pre-treatment anxiety symptoms (OR = 1.26, 95% CI 1.15–1.38).
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.

Abbreviations: ACE-27, adult comorbidity evaluation; CI, confidence interval; ECOG, Eastern cooperative oncology group; EORTC QLQ-H&N35, European organization for research and treatment of cancer quality of life questionnaire - HNC-specific module; HADS, hospital anxiety and depression scale; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital anxiety and depression scale, depression subscale; HNC, head and neck cancer; NET-QUBIC, the Netherlands quality of life and biomedical cohort; PSQI, Pittsburgh sleep quality index; SD, standard deviation; UCL, Utrecht coping list.

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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 timepoints) 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.

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 (Fig. 1).

Determinants of sleep quality trajectories

Univariate analyses (Table 2) showed that patients in the different trajectories of sleep quality differed in sex ($P < 0.001$), the extent of passive coping ($P < 0.001$), pretreatment painkiller use ($P < 0.001$), 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 ($P < 0.001$), feeling ill ($P < 0.001$), depression symptoms ($P < 0.001$), and anxiety symptoms ($P < 0.001$). 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 ($P < 0.001$) 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 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)	0.08
Female	105 (25.5%)	85 (26.0%)	0.93
Education level[b]			
Low	151 (38.6%)	128 (49.8%)	0.01
Middle	106 (27.1%)	65 (25.3%)	
High	134 (34.3%)	64 (24.9%)	
Living alone[b]	74 (18.9%)	90 (35.0%)	<0.001
HNC location			
Oral cavity	116 (28.2%)	83 (25.4%)	0.14
Oropharynx	144 (35.0%)	118 (36.1%)	
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%)	0.12
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%)	<0.001
1 or more	97 (23.5%)	135 (41.3%)	
Comorbidity[b]			
None	141 (35.4%)	63 (20.9%)	<0.001
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%)	0.24
Combination treatment	184 (44.7%)	161 (49.2%)	

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

[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.

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

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)	0.06
Sex							
Male	307 (74.5%)	128 (82.6%)*	38 (84.4%)	44 (81.5%)	46 (67.6%)	51 (56.7%)*	<0.001
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%)	0.77
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%)	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)	0.11
Palliative reaction	9.4 (3.6)	9.1 (4)	9.3 (3)	9.5 (3)	9.7 (4)	9.7 (4)	0.66
Avoidance coping	7.1 (3.3)	7.0 (3)	6.8 (3)	7.3 (3)	7.3 (3)	7.0 (3)	0.90
Seeking social support	6.9 (3.2)	6.6 (3)	7.2 (3)	7.4 (3)	7.3 (3)	6.9 (4)	0.37
Passive coping	3.2 (2.6)	2.4 (2)*·†	3.1 (2)	3.1 (3)	3.8 (3)*	4.1 (3)†	<0.001
Expression of emotions	1.8 (1.4)	1.7 (1)	1.8 (1)	1.9 (1)	1.9 (1)	2.1 (1)	0.15
Comforting thoughts	7.2 (2.5)	7.0 (2)	7.4 (2)	7.3 (2)	7.4 (3)	7.4 (3)	0.61
Comorbidity[b]							
None to mild	301 (75.6%)	121 (80.7%)	33 (75.0%)	35 (66.0%)	49 (77.8%)	63 (71.6%)	0.23
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%)	0.73
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%)	0.48
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%)	0.27
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%)	0.37
Combination treatment	184 (44.7%)	66 (42.6%)	20 (44.4%)	23 (42.6%)	38 (55.9%)	37 (41.1%)	
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%)	0.36
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%)	0.38
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)	0.02
Swallowing problems	13 (19)	10 (18)	18 (21)	11 (19)	16 (19)	16 (20)	0.046
Sense problems	7 (15)	6 (13)	8 (15)	8 (19)	10 (17)	6 (15)	0.36
Speech problems	18 (11)	16 (23)	17 (18)	17 (24)	23 (27)	16 (19)	0.29
Problems with social eating	10 (16)	6 (12)*	11 (19)	10 (19)	16 (19)*	11 (16)	0.001
Problems with social contact	4 (9)	2 (7)	4 (8)	3 (8)	6 (13)	5 (10)	0.08
Less sexual interest and enjoyment	26 (31)	18 (27)*	30 (25)	21 (31)	32 (33)	35 (34)*	<0.001
Teeth problems	14 (26)	12 (24)	13 (26)	12 (25)	18 (31)	17 (27)	0.30
Problems with opening mouth	11 (24)	11 (22)	10 (22)	5 (18)	14 (27)	13 (29)	0.28
Dry mouth	15 (22)	11 (20)	13 (23)	15 (22)	17 (23)	18 (24)	0.14
Sticky saliva	12 (22)	9 (20)	19 (26)	13 (22)	13 (23)	13 (20)	0.09
Coughing	21 (24)	17 (22)	26 (25)	24 (25)	22 (25)	24 (26)	0.10
Feeling ill	11 (21)	5 (14)*·†‡	18 (23)*	11 (22)	16 (25) †	14 (22)‡	<0.001
Used painkillers, n (%)	202 (49.8%)	56 (36.6%)*	26 (59.1%)	23 (44.2%)	35 (52.2%)	62 (68.9%)*	<0.001
Used nutritional supplements, n (%)	51 (12.5%)	13 (8.4%)	6 (13.3%)	8 (15.4%)	11 (16.2%)	13 (14.4%)	0.42
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%)	0.24
Had weight gain, n (%)	34 (8.4%)	12 (7.8%)	2 (4.5%)	7 (13.5%)	2 (3.1%)	11 (12.4%)	0.14

(*continued on next page*)

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)†	<0.001
HADS-D > 7	57 (13.9%)	12 (7.8%)*	5 (11.1%)	8 (15.4%)	13 (19.1%)	19 (21.1%)*	0.03
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)‡; §	<0.001
HADS-A > 7	109 (26.7%)	19 (12.3%)*;†	12 (26.7%)	9 (17.3%)‡	25 (37.3%)*	44 (48.9%)†;‡	<0.001

*, †, ‡, 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.

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.

[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.

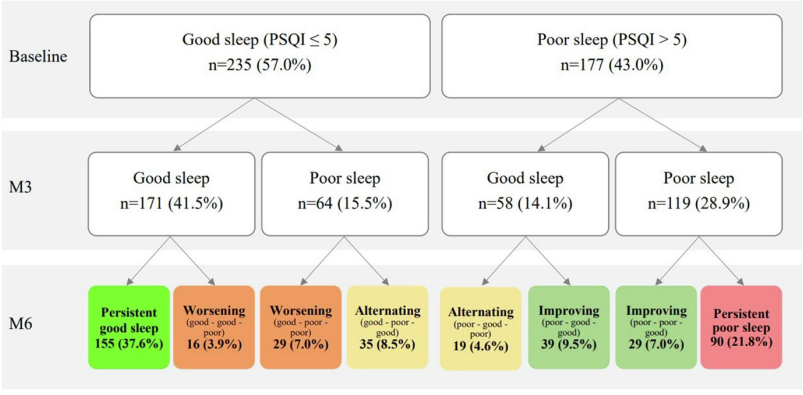

Fig. 1. Sleep quality at baseline, 3-month, and 6-month after treatment. Abbreviations: PSQI, Pittsburgh sleep quality index.

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

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	Alternating sleep quality	Poor sleep, improving	Persistent poor sleep	P value
	n = 41 (10.8%)	n = 46 (12.1%)	n = 64 (16.9%)	n = 81 (21.4%)	
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)	0.02
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)	0.03
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)	0.03
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)	<0.001

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

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.

Data availability statement

The data underlying this article is regulated by the NETherlands Quality of life and Biomedical Cohort study in head and neck cancer (NET-QUBIC) project. Data will be shared upon request addressed to the NET-QUBIC principal investigator.

Declaration of Competing Interest

None.

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