Received: 22 March 2021 | Revised: 5 October 2021 | Accepted: 1 November 2021

DOI: 10.1002/hed.26930

ORIGINAL ARTICLE

WILEY

Prevalence of neurocognitive and perceived speech deficits in patients with head and neck cancer before treatment: Associations with demographic, behavioral, and disease-related factors

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Funding information
the Dutch Cancer Society

Section Editor: Allen Sherman

Abstract

Background: Neurocognition and speech, relevant domains in head and neck cancer (HNC), may be affected pretreatment. However, the prevalence of pretreatment deficits and their possible concurrent predictors are poorly understood.

Methods: Using an HNC prospective cohort (Netherlands Quality of Life and Biomedical Cohort Study, $N \geq 444$) with a cross-sectional design, we investigated the estimated prevalence of pretreatment deficits and their relationship with selected demographic, behavioral, and disease-related factors.

Results: Using objective assessments, rates of moderate-to-severe neurocognitive deficit ranged between 4% and 8%. From patient-reported outcomes, 6.5% of patients reported high levels of cognitive failures and 46.1% reported speech deficits. Patient-reported speech functioning was worse in larynx compared to other subsites. Other nonspeech outcomes were unrelated to any variable. Patient-reported neurocognitive and speech functioning were modestly correlated, especially in the larynx group.

Conclusions: These findings indicate that a subgroup of patients with HNC shows pretreatment deficits, possibly accentuated in the case of larynx tumors.

KEYWORDS

fluency, head and neck cancer, neurocognitive assessment, pretreatment symptoms

1 | BACKGROUND

Head and neck cancer (HNC) and its treatment may affect both neurocognitive and speech functioning.[1–7] Although neurocognition and speech are commonly studied separately in HNC, they may be highly intertwined from the patients' perspective,[8] as speaking spans a continuum of neurocognitive functions, such as retrieval of information from memory and executive functioning, to articulation.[9]

Recently, studies have shown that patients with HNC may already present with speech and neurocognitive deficits pretreatment.[8,10,11] Here, speech refers to motor aspects of speaking, such as articulation, voice, and speech quality, as opposed to "language," which would refer to the nonmotor aspects of speaking (e.g., failures to retrieve information from memory resulting in word finding problems). Speech deficits may be present before the beginning of treatment because of the damage to the organs and muscles involved in speaking.[12] In a previous report of the multicenter Netherlands Quality of Life and Biomedical Cohort Study (NET-QUBIC)[13] including 254 patients pretreatment, we found between 5% and 15% of patients had moderate-to-severe neurocognitive impairment and 43% of patients had speech impairment.[8] Moreover, patient-reported outcome measures of speech and neurocognition were modestly correlated.[8] Possible concurrent predictors of pretreatment neurocognitive and speech impairments have, however, remained unclear. Furthermore, *chronic* alcohol intake and tobacco use, well-known risk factors for HNC and in particular for oral and laryngeal cancer,[14] may have detrimental effects on neurocognitive function.[15–18] Note that these latter findings are not based on a populations with head and neck cancer. However, due to relatively small sample sizes in previous studies,[10,11] including our own,[8] it is unclear how pretreatment neurocognitive functioning differs across different tumor subsites and to what extent chronic alcohol and tobacco use contribute to poor neurocognitive functioning in these tumor subgroups.

Using the largest prospective cohort with neurocognitive and speech assessments to date (NET-QUBIC)[13] and extending our previous findings (via expansion of the dataset we previously analyzed, from $N = 254$ to $N \geq 444$),[8] here we sought to evaluate the estimated prevalence of patient-reported speech problems, and of patient-reported and selected objectively measured neurocognitive deficits pretreatment. Moreover, we examined whether tumor subsite, TNM tumor stage, chronic alcohol intake, chronic tobacco use, or the interaction between tumor subsite and alcohol and tobacco relate to pretreatment speech and neurocognitive functioning beyond demographic variables. Finally, using a larger sample relative to our previous study,[8] we aimed to replicate the finding that patient-reported neurocognitive and speech measures are correlated.

2 | METHODS

2.1 | Sample

Recruitment was performed in eight HNC centers in the Netherlands in the context of the NET-QUBIC study. Patients were approached for participation shortly after diagnosis, and before start of treatment. The accrual rate was 40%. Reasons for not participating were mainly feeling psychologically incapable (29%) among other reasons (see Verdonck-de Leeuw et al.[13] for all details). All included individuals in the NET-QUBIC study had a newly diagnosed HNC (oral, oropharynx, hypopharynx, larynx, and neck metastasis of unknown primary tumor with proven squamous cell carcinoma histology; all TNM stages), previously untreated and planned for treatment with curative

TABLE 1 Characteristics of the sample, restricted to the patients who completed all patient-reported and neurocognitive assessments, and those who did not complete all tests

Variable		Completed all tests, $N = 410$ (%)	Did not complete all tests, $N = 329$ (%)	Comparison (excluding missing)
Age	Mean, median (SD)	63.7, 64 (8.8)	62.7, 63 (10.8)	$t(624) = 1.41$, $p = 0.189$
Sex	Men	312 (76)	237 (72)	$X^2(1) = 1.37$, $p = 0.241$
	Women	98 (24)	92 (28)	
Education level	Low	173 (42)	106 (32)	$X^2(2) = 2.12$, $p = 0.346$
	Medium	116 (28)	55 (17)	
	High	121 (30)	77 (23)	
	Missing	0	91 (28)	
Tumor stage	Stage I	98 (24)	64 (19)	$X^2(3) = 2.55$, $p = 0.466$
	Stage II	69 (17)	64 (19)	
	Stage III	68 (17)	59 (18)	
	Stage IV	175 (43)	142 (43)	
Tumor site	Hypopharynx	23 (6)	29 (9)	$X^2(4) = 4.09$, $p = 0.394$
	Larynx	116 (28)	89 (27)	
	Oral cavity	106 (26)	93 (28)	
	Oropharynx	153 (37)	109 (33)	
	Unknown	12 (3)	9 (3)	
Smoking status	Not a (current) daily smoker	312 (76)	133 (40)	$X^2(1) = 1.61$, $p = 0.205$
	Daily smoker	97 (24)	30 (9)	
	Missing	1 (0.2)	166 (50)	
Alcohol consumption	Excessive consumption	89 (22)	40 (12)	$X^2(1) = 0.23$, $p = 0.629$
	No excessive consumption	319 (78)	126 (38)	
	Missing	2 (0.5)	163 (50)	
WHO performance status (grade)	Fully active (0)	291 (71)	216 (66)	$X^2(3) = 6.07$, $p = 0.108$ (excluding grade 4)
	Restricted but ambulatory (1)	103 (25)	88 (27)	
	Ambulatory, unable of work (2)	16 (4)	24 (7)	
	Limited self-care (3)	0 (0)	1 (0)	
	Completely disabled (4)	0 (0)	0 (0)	
Comorbidity	Severe	38 (9)	38 (12)	$X^2(3) = 7.91$, $p = 0.048$
	Moderate	76 (19)	79 (24)	
	Mild	148 (36)	116 (35)	
	None	128 (31)	76 (23)	
	Missing	20 (5)	20 (6)	

Note: Age was tested with an independent samples *t* test, the distributions of the other categorical-dependent variables were tested with chi-square tests.

intent ($N = 739$ for the entire NET-QUBIC cohort). All participating patients signed a written consent. Patients' characteristics are presented in Table 1. The cross-sectional sample reported here ($N \geq 444$) partly overlaps with our previous study[8] (being a larger dataset than the initially analyzed sample of $N = 254$, enabling more in-depth analysis). Appropriate statistical procedures were followed as a result.[19]

2.2 | Assessments and procedure

Clinical and demographic characteristics and alcohol and tobacco use were collected via medical records and self-report questionnaires, respectively. Two items of the 13-item study-specific patient-reported questionnaire were used to assess smoking status and nicotine dependence.[13] Patients were categorized as "current smokers" or as "not current smokers." This latter included those who never smoked (i.e., less than 100 units in their lifetime) or stopped smoking (daily). Four items of the 21-item study-specific questionnaire were used to assess alcohol intake and dependence. Patients were categorized as having "excessive alcohol consumption (yes/no)" according to the definition of excessive drinking of the National Institute for Public Health and the Environment (https://www.rivm.nl/). According to the definition, women who drink more than 14 or men who drink more than 21 units of alcohol per week are considered to have excessive alcohol consumption. Comorbidity scores were defined according to the Adult Comorbidity Evaluation-27 (ACE-27)[20] and performance status according to the grades from the World Health Organization. Level of education was classified as high (university or higher professional education), medium (senior or higher general secondary education), or low (primary education, lower or preparatory vocational education, or intermediary general secondary education), following the Dutch educational system.

Two patient-reported outcome measures (PROM) were used. The Cognitive Failures Questionnaire[21] (CFQ) assesses self-perceived neurocognitive functioning (PROM-neurocognitive henceforth), with 25 questions about experienced failures in perception, attention, memory, and so on (e.g., "Do you fail to notice signposts on the road?"). Available norms for the Dutch population exist based on 1,358 community dwelling individuals aged between 24 and 81 years covering all education levels.[22] Higher CFQ scores indicate more perceived failures with a normal score between 21 and 43, high scores between 44 and 54 (>1 to <2 SD) and very high scores above 54 (≥2 SD), compared to a normative sample's mean. The Speech Handicap Index[23] (SHI) was used for self-perceived speech functioning (PROM-speech, henceforth), with 30 items probing speech problems (e.g., "My articulation is unclear," "My speech problem upsets me"). Available norms for the Dutch population exist based on 111 controls and 104 individuals with HNC.[23] Higher SHI scores indicate more speech problems (with a maximum of 120); a cut-off of 6 corresponds to daily-life mild-to-severe problems. The SHI is focused on speech problems and its psychological impact and, as such, is not a valid instrument to study language problems.

The neuropsychological battery[24] contained the following assessments: the Trail Making Test[25] (TMT-A, providing a measure of processing speed; TMT-B: providing a measure of executive function; both do not require any speech output), the Hopkins Verbal Learning Test[26] (HVLT, based on 12 words, providing a measure of episodic verbal learning and memory), and the Controlled Oral Word Association Test[27] (COWAT, phonemic-based, providing a measure of verbal fluency). Note that, for verbal memory, only the delayed recall measure was used, as this measure better reflects performance for verbal memory with less confounding factors such as attention, working memory, and speech rate.[24] The neuropsychological battery was administered by trained assessors at hospitals and/or patients' homes. For the objective measures, we used available normative data to obtain standardized T-scores (mean = 50, SD = 10), adjusted for demographic variables. For the TMT[28] and HVLT,[29] the scores were adjusted for age, sex, and education. For COWAT, the scores were adjusted for education (norms derived from own databases). Then, for each test separately, we quantified the number of patients performing *below* the adjusted norm (unimpaired: ≤1 SD, mild-to-moderate: >1 to <2 SD, moderate-to-severe: ≥2 SD, compared to the appropriate normative mean). More detailed information on the NET-QUBIC general study's protocol is presented elsewhere.[13]

2.3 | Analyses

Since not all individuals completed all assessments (see Table 1), missing data were identified and for each analysis reported below, only complete cases for that specific analysis were included (e.g., a patient contributed data for a correlation between variables *A* and *B* if those data were present, regardless of the missingness of this patient's data on variable *C*). Sample sizes (*N*) are reported for each analysis separately.

Multiple linear regression models were used to assess the relative contribution of selected demographic, behavioral, and disease-related variables to patient-reported and objectively measured scores. All tests were 2-tailed. The following independent variables were used: age (continuous), sex (categorical, "men" as reference level), education (categorical: low, medium, high, "high" as reference level), tumor site ("larynx" as reference level), TNM tumor stage (categorical, TNM stage I as reference level), current alcohol consumption (categorical: excessive or not excessive, "not excessive" as reference level), smoking status (categorical, "not a (current) daily smoker" as reference level), and the interaction between tumor subsite and current alcohol consumption, and

tumor subsite and smoking status. For the objective neuropsychological measures, since standardized values were used adjusted for the relevant demographic variables, the models only included tumor site and TNM stage, current alcohol consumption, smoking status, and the interactions mentioned above.

Finally, to examine the relationship between the two PROMs (self-reported speech and cognitive functioning),

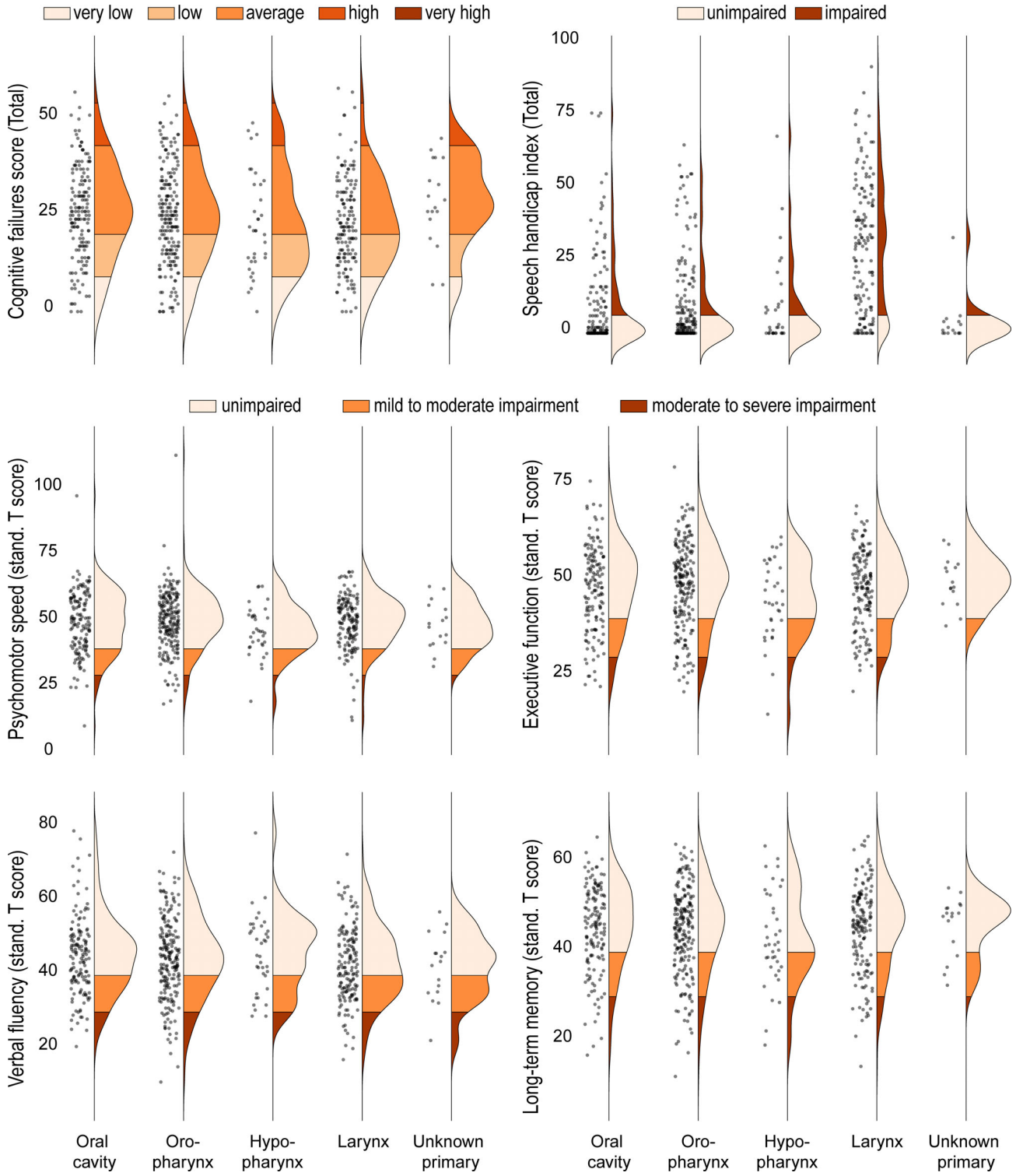

FIGURE 1 Distributions of scores for each tumor subsite on patient-reported (raw scores) and objective neurocognitive measures (standardized T scores). Colors indicate score categories. Each dot represents the score of an individual. Dots are randomly displaced in the horizontal axis for display purposes only [Color figure can be viewed at wileyonlinelibrary.com]

between PROM-neurocognitive and objective neurocognitive measures, and between PROM-speech and verbal fluency (the neuropsychological measure requiring most language production), Spearman correlations were calculated for each tumor subsite separately, 2-tailed, Holm–Bonferroni corrected. All analyses were conducted in R.[30] Given the risk of increased false-positive rates from analyzing partly overlapping samples, we used a correction procedure that lowers the alpha-level of all tests conducted.[19] Thus, for all main analyses in the study, an alpha-level of 0.01 was considered. Interactions were followed-up on by means of simple slope analyses, and evaluated at an alpha level of 0.05 given that they were not previously examined by previous studies using a partly overlapping sample.

3 | RESULTS

Table 1 shows the characteristics of the sample, for the group of patients who completed all patient-reported and neurocognitive assessments ($N = 410$) and for the group that did not complete all assessments ($N = 329$). The distributions between those who did and did not complete all assessments were similar for demographic, behavioral, and disease-related factors (all ps > 0.1), except for comorbidity (based on Pearson residuals, the biggest contribution to this outcome is that the count of "no comorbidity" in the group not completing all assessments is lower than expected; note that missing data were not included in these comparisons). Due to the analysis-specific selection of data to deal with missing data, the sample sizes N are reported below for each analysis separately.

Distributions of PROM-neurocognitive and PROM-speech are shown in Figure 1. For PROM-neurocognitive, 6.5% of the patients experienced high levels of perceived cognitive failures and 0.7% very high levels[22] (based on $N = 568$). For PROM-speech, 46.1% of the patients reported speech problems in daily life (based on $N = 540$), similar to previous studies assessing patients prior to starting treatment.[31,32] For the neuropsychological tests, 12.8% of the patients were mild-to-moderately impaired in processing speed and 16.8% in executive functioning (both based on $N = 553$), 19.9% in episodic memory, and 26.2% in verbal fluency (both based on $N = 569$). Four percent of the patients had moderate-to-severe impairment for processing speed, 5.6% for executive functioning, 7.6% for delayed recall, and 7.9% for verbal fluency. These rates of moderate-to-severe impairment are higher compared to the norm (i.e., by definition, 2.3% of the population performs ≤2 SDs below the normative mean).

For PROM-speech functioning (total Speech Handicap Index, SHI), the model explained 22% of the variance ($p < 0.001$, based on $N = 492$) (Table 2). PROM-speech functioning was associated with sex (worse in men, $p < 0.005$), tumor subsite (ps < 0.001), alcohol use ($p < 0.005$), and subsite-by-alcohol interactions (ps < 0.01). Overall, the larynx group had the worst PROM-speech functioning scores, which differed significantly from all other groups (ps < 0.001). Regarding alcohol use, we found that those with no current excessive alcohol consumption experienced worse PROM-speech functioning (no current consumption SHI mean = 15, median = 5, SD = 20, range = 0–92; excessive consumption SHI mean = 13, median = 3, SD = 17, range = 0–60; $p = 0.002$). Regarding the subsite-by-alcohol interaction, we found that the effect of excessive alcohol use was particularly prominent in the larynx group compared to the oropharynx group ($p \leq 0.006$). To further probe this interaction, we ran linear regression models for each tumor subsite separately with alcohol consumption as the independent variable. In these separate analyses, the effect of alcohol consumption was significant only in the group with larynx tumors (unstandardized estimate $= -10.34$, $t = -2.44$, $p = 0.016$), but not in the groups with other tumor subsites (all ps > 0.370).

It could be argued that the finding regarding alcohol consumption is confounded by the fact that those without current excessive alcohol consumption could have excessively consumed alcohol in the past. To address this question, we split the group with no current excessive alcohol consumption into two categories, based on our questionnaire: Those who never reported excessive alcohol consumption versus those who reported having consumed alcohol excessively in the past. The total Speech Handicap Index scores did not differ between the group without a history of excessive alcohol consumption (median and mean SHI = 5 and 16, SD = 21, range = 0–91) and the group with a history of excessive alcohol use (median and mean SHI = 5 and 14.7, SD = 19, range = 0–83, $t(378) = -0.692$, $p = 0.489$).

For the PROM-neurocognitive functioning (total CFQ, based on $N = 512$) (Table 2) and the objective measures (Table 3) of processing speed (TMT-A, based on $N = 444$), executive functioning (TMT-B, based on $N = 444$), and episodic memory (HVLT delayed recall, based on $N = 454$), the explained variance of the models was in general low (1.5% at most) and none of the models was statistically significant (all ps > 0.130). Objectively measured verbal fluency (COWAT, based on $N = 452$) was associated with tumor subsite (worse in the larynx subgroup than in the oral cavity and oropharynx subgroups, ps < 0.01) (Figure 1 and Table 3), although the explained variance of the regression model was also low

TABLE 2 Multiple linear regression regarding associations of self-reported speech handicap (SHI) and cognitive failures (CFQ) with selected demographic, behavioral, and disease-related characteristics

	Speech handicap Unst. beta (95% CI)	Cognitive failures Unst. beta (95% CI)
Intercept	40.94*** (29.01, 52.88)	14.83*** (6.59, 23.07)
Age	−0.14 (−0.31, 0.03)	0.10 (−0.02, 0.216)
Sex	−5.47** (−9.26, −1.68)	1.92 (−0.70, 4.55)
Education: medium (vs. high)	−1.19 (−5.26, 2.87)	2.82 (−0.02, 5.66)
Education: low (vs. high)	1.30 (−2.47, 5.07)	3.03 (0.42, 5.63)
Subsite: oral cavity (vs. larynx)	−19.86*** (−25.06, −14.66)	3.36 (−0.21, 6.94)
Subsite: oropharynx (vs. larynx)	−21.08*** (−26.59, −15.58)	3.70 (−0.13, 7.53)
Subsite: hypopharynx (vs. larynx)	−22.65*** (−32.74, −12.55)	−0.16 (−7.23, 6.92)
Subsite: unknown primary (vs. larynx)	−24.68*** (−36.49, −12.86)	7.40 (−1.06, 15.87)
Stage II (vs. I)	−0.06 (−4.98, 4.87)	−2.49 (−5.89, 0.90)
Stage III (vs. I)	3.39 (−1.83, 8.60)	−0.73 (−4.34, 2.88)
Stage IV (vs. I)	−1.59 (−6.34, 3.17)	−1.90 (−5.12, 1.34)
Excessive alcohol consumption	−10.58** (−17.25, −3.91)	1.11 (−3.49, 5.70)
Daily smoking	−0.20 (−6.95, 6.55)	−2.51 (−7.23, 2.21)
Subsite: oral cavity (vs. larynx) * excessive alcohol consumption	7.39 (−3.21, 17.98)	−0.68 (−8.07, 6.71)
Subsite: oropharynx (vs. larynx) * excessive alcohol consumption	13.14* (3.82, 22.47)	−0.03 (−6.38, 6.33)
Subsite: hypopharynx (vs. larynx) * excessive alcohol consumption	1.74 (−13.76, 17.23)	4.73 (−5.78, 15.23)
Subsite: unknown primary (vs. larynx) * excessive alcohol consumption	7.81 (−19.43, 35.04)	−3.06 (−17.83, 11.70)
Subsite: oral cavity (vs. larynx) * daily smoking	−1.05 (−12.05, 9.96)	3.59 (−4.05, 11.24)
Subsite: oropharynx (vs. larynx) * daily smoking	−1.93 (−10.998, 7.141)	−1.33 (−7.64, 4.97)
Subsite: hypopharynx (vs. larynx) * daily smoking	11.807 (−3.36, 26.97)	0.75 (−9.65, 11.15)
Subsite: unknown primary (vs. larynx) * daily smoking	−3.31 (−26.46, 19.83)	1.98 (−12.56, 16.55)
Observations	492	512
Adjusted R^2	0.22	0.02
Residual standard error	17.16 ($df = 470$)	12.17 ($df = 490$)
F statistic	7.64 ($df = 21; 470$)	1.36 ($df = 21; 490$)
p value	<0.001	0.13

Note: 95% confidence intervals (CI) provided in parentheses below the unstandardized beta coefficients. Higher speech handicap and cognitive failures scores indicate more perceived problems.
*$p < 0.01$; **$p < 0.005$; ***$p < 0.001$.

(1.4%, $p = 0.137$). The effect sizes for verbal fluency for the comparison between the larynx and oral cavity, and larynx and oropharynx, were $d = 0.425$ and $d = 0.453$, respectively. We note that these effects should be interpreted with caution given that the regression model is not significant.

Objective and PROM-neurocognitive measures were not correlated ($ps > 0.4$), consistent with findings

reported in previous studies for various populations[10,33] (Table 4; see also Supporting Information for scatterplots). Verbal fluency was not correlated with PROM-speech for any tumor subgroup ($ps > 0.5$). The PROM-neurocognitive measure correlated with the PROM-speech measure with a small effect size for the

TABLE 3 Multiple linear regression regarding associations of neuropsychological test scores with selected behavioral and disease-related characteristics

	TMT-A Unst. beta (95% CI)	TMT-B Unst. beta (95% CI)	Fluency Unst. beta (95% CI)	Delayed recall Unst. beta (95% CI)
Intercept	50.31*** (47.48, 53.14)	48.78*** (46.08, 51.48)	43.08*** (40.54, 45.62)	45.59*** (43.22, 47.97)
Subsite: oral cavity (vs. larynx)	−0.63 (−4.09, 2.83)	0.17 (−3.14, 3.47)	4.34* (1.21, 7.46)	0.79 (−2.12, 3.70)
Subsite: oropharynx (vs. larynx)	−0.46 (−4.17, 3.24)	1.91 (−1.63, 5.45)	4.63* (1.30, 7.95)	−1.93 (−5.04, 1.18)
Subsite: hypopharynx (vs. larynx)	−4.07 (−11.36, 3.23)	−5.83 (−12.79, 1.13)	3.22 (−3.29, 9.73)	1.08 (−5.02, 7.17)
Subsite: unknown primary (vs. larynx)	−0.59 (−8.39, 7.21)	0.07 (−7.38, 7.51)	0.65 (−6.40, 7.70)	0.52 (−6.08, 7.12)
Stage II (vs. I)	−0.10 (−3.42, 3.23)	0.06 (−3.11, 3.23)	−1.39 (−4.38, 1.59)	0.69 (−2.11, 3.48)
Stage III (vs. I)	1.50 (−1.97, 4.97)	0.30 (−3.01, 3.61)	−1.01 (−4.14, 2.12)	−0.74 (−3.67, 2.18)
Stage IV (vs. I)	1.75 (−1.40, 4.90)	0.03 (−2.98, 3.03)	−3.12 (−5.97, −0.28)	1.92 (−0.73, 4.57)
Excessive alcohol consumption	0.31 (−4.00, 4.62)	1.08 (−3.04, 5.19)	1.89 (−2.01, 5.79)	2.07 (−1.54, 5.69)
Daily smoking	−1.36 (−5.84, 3.12)	−1.50 (−5.77, 2.78)	−0.29 (−4.22, 3.64)	−0.51 (−4.19, 3.16)
Subsite: oral cavity (vs. larynx) * excessive alcohol consumption	0.37 (−6.74, 7.47)	0.22 (−6.55, 7.00)	0.08 (−6.36, 6.52)	−0.93 (−6.93, 5.08)
Subsite: oropharynx (vs. larynx) * excessive alcohol consumption	1.57 (−4.51, 7.65)	−2.59 (−8.38, 3.21)	0.71 (−4.80, 6.21)	−0.25 (−5.37, 4.87)
Subsite: hypopharynx (vs. larynx) * excessive alcohol consumption	1.34 (−9.13, 11.80)	0.59 (−9.39, 10.58)	−1.51 (−10.35, 7.33)	−7.93 (−16.19, 0.33)
Subsite: unknown primary (vs. larynx) * excessive alcohol consumption	0.01 (−14.69, 14.71)	1.12 (−12.90, 15.15)	4.26 (−9.05, 17.57)	−8.69 (−21.15, 3.76)
Subsite: oral cavity (vs. larynx) * daily smoking	2.82 (−4.52, 10.15)	−1.07 (−8.07, 5.92)	1.15 (−5.42, 7.71)	−2.23 (−8.37, 3.90)
Subsite: oropharynx (vs. larynx) * daily smoking	−2.48 (−8.58, 3.62)	−4.74 (−10.56, 1.08)	−3.00 (−8.44, 2.43)	−1.29 (−6.37, 3.79)
Subsite: hypopharynx (vs. larynx) * daily smoking	−2.97 (−13.42, 7.48)	5.33 (−4.65, 15.30)	5.06 (−3.80, 13.92)	0.99 (−7.31, 9.29)
Subsite: unknown primary (vs. larynx) * daily smoking	−5.38 (−18.85, 8.09)	3.61 (−9.24, 16.46)	5.91 (−6.24, 18.07)	−0.43 (−11.81, 10.95)
Observations	444	444	452	454
Adjusted R^2	−0.01	−0.00	0.01	−0.00
Residual standard error	11.05 ($df = 426$)	10.54 ($df = 426$)	10.01 ($df = 434$)	9.37 ($df = 436$)
F statistic	0.75 ($df = 17; 426$)	0.97 ($df = 17; 426$)	1.39 ($df = 17; 434$)	0.91 ($df = 17; 436$)
p value	0.751	0.497	0.137	0.562

Note: 95% confidence intervals are provided in parentheses below the unstandardized beta coefficients. Lower scores indicate poorer performance.
*$p < 0.01$; ***$p < 0.001$.

TABLE 4 Spearman's rank correlation coefficient (ρ) and corresponding p values (without and with correction using the Holm–Bonferroni method) for associations of assessment scores per tumor subsite

Tumor subsite	Variable 1	Variable 2	ρ	p	Corrected p	N
Oral cavity	CFQ	Fluency	0.079	0.399	1	115
Oropharynx	CFQ	Fluency	−0.000	0.998	1	165
Hypopharynx	CFQ	Fluency	0.450	0.023	0.618	25
Larynx	CFQ	Fluency	0.066	0.456	1	128
Unknown primary	CFQ	Fluency	−0.097	0.741	1	14
Oral cavity	CFQ	Recall	−0.058	0.539	1	116
Oropharynx	CFQ	Recall	−0.042	0.589	1	165
Hypopharynx	CFQ	Recall	−0.100	0.624	1	25
Larynx	CFQ	Recall	−0.023	0.799	1	129
Unknown primary	CFQ	Recall	−0.097	0.742	1	14
Oral cavity	CFQ	TMT-A	−0.048	0.608	1	116
Oropharynx	CFQ	TMT-A	−0.150	0.061	1	162
Hypopharynx	CFQ	TMT-A	−0.110	0.601	1	24
Larynx	CFQ	TMT-A	0.020	0.827	1	123
Unknown primary	CFQ	TMT-A	−0.004	0.988	1	14
Oral cavity	CFQ	TMT-B	−0.000	0.997	1	116
Oropharynx	CFQ	TMT-B	−0.027	0.737	1	162
Hypopharynx	CFQ	TMT-B	0.050	0.818	1	24
Larynx	CFQ	TMT-B	−0.041	0.653	1	123
Unknown primary	CFQ	TMT-B	−0.300	0.306	1	14
Oral cavity	Fluency	SHI	−0.110	0.270	1	109
Oropharynx	Fluency	SHI	0.023	0.775	1	160
Hypopharynx	Fluency	SHI	0.340	0.109	1	24
Larynx	Fluency	SHI	0.150	0.111	1	122
Unknown primary	Fluency	SHI	−0.400	0.171	1	13
Oral cavity	CFQ	SHI	0.210	0.010	0.272	144
Oropharynx	CFQ	SHI	0.330	<0.001	<0.001	190
Hypopharynx	CFQ	SHI	0.260	0.144	1	33
Larynx	CFQ	SHI	0.340	<0.001	<0.001	147
Unknown primary	CFQ	SHI	0.240	0.382	1	15

Note: Higher rho values indicate a stronger association between the ranks of the two implicated variables. Abbreviations: CFQ, Cognitive Failures Questionnaire score (higher scores indicate more perceived failures); Fluency, Controlled Oral Word Association Test score (standardized, higher values indicate better performance); Recall, Hopkins Verbal Learning Test delayed recall score (standardized, higher values indicate better performance); TMT-A, Trail Making Test – Part A (standardized, higher values indicate better performance); TMT-B, Trail Making Test – Part B (standardized, higher values indicate better performance); SHI, Speech Handicap Index score (higher scores indicate more speech problems).

oropharynx subgroup (based on $N = 190$, $\rho = 0.33$, $p < 0.001$) and larynx subgroup (based on $N = 147$, $\rho = 0.34$, $p < 0.001$), similar to observations in our previous study, which included about one-third of the same participants.[8] By contrast, the PROM-neurocognitive measure was not correlated with the PROM-speech measure for the oral cavity, hypopharynx, and unknown primary subgroups (ps > 0.271).

4 | DISCUSSION

Neurocognitive and speech functioning may be affected by HNC already prior to treatment,[8,10–12,31] but concurrent predictors of impairment in these domains are currently unclear. Using the largest prospective cohort with neurocognitive and speech assessments to date (NET-QUBIC),[13] we were able to estimate the prevalence of

problems in patient-reported and objectively measured neurocognitive and speech functioning, examine whether selected behavioral and disease-related factors are associated with functioning in these domains, and determine whether patient-reported outcome measures of neurocognition and speech are correlated.

The estimated prevalence of pretreatment self-reported cognitive failures was 1%–7%, which is lower than in the normal population (for whom about 2.5%–15% is expected), but similar to what has been reported previously, for example in a group of newly diagnosed patients with oropharyngeal cancer assessed prior to treatment.[11] However, another study that compared a group with HNC before treatment with a control group without a cancer diagnosis initially found worse self-perceived neurocognitive functioning in the HNC group, but after adjustment for fatigue, anxiety, and depression, the differences between the two groups were no longer present.[34] The reason for these findings is unclear and likely a complex one, which our study on its own is not able to resolve. The estimated prevalence of self-reported speech deficits was 46%, which is higher than in the normal population. Previous studies assessing self-reported speech functioning prior to treatment in newly diagnosed patients with HNC have found similar or higher estimated prevalence, for example between 62%[31] and 100%.[32] Regarding the objective performance measures of neurocognition, we found that the estimated prevalence of pretreatment mild-to-moderate and moderate-to-severe neurocognitive impairment was 13%–26% and 4%–8%, respectively, which is higher than in the normal population. The estimated prevalence we observed is largely in agreement with previous studies. For example, in a group of newly diagnosed patients with oropharyngeal cancer, the estimated prevalence of pretreatment mild-to-moderate neurocognitive impairment was around 9% and moderate-to-severe impairment was around 2%.[11] Another study assessing newly diagnosed patients with HNC observed a prevalence of between 12% and 20% for mild-to-moderate and 2% and 7% for moderate-to-severe neurocognitive impairment at baseline.[10] Importantly, however, the study that included a control group without cancer in addition to a group with HNC before treatment concluded that the estimated prevalence of neurocognitive impairment was similar in both the group with HNC and the control group.[34] Given that baseline neurocognitive impairment may be associated with the quality of life, hamper patient–clinician interaction, and affect treatment adherence,[35,36] it is important to understand pretreatment neurocognitive impairment in this population and firmly establish whether its estimated prevalence is higher than in the normal population. For that, large-scale studies performing a comparison with a control group without a cancer diagnosis,[34] as well as with groups of patients with other cancer types would be invaluable.

Our results agree with recent evidence on the reality of pretreatment cancer-related neurocognitive impairment.[37] The impairment, which should be replicated in independent samples, is not readily explained by age, sex, education, TNM tumor stage, chronic smoking, or alcohol consumption. However, perceived deficits in speech seem to occur more often in the larynx cancer group. This was found for the self-reported measure of speech functioning (Speech Handicap Index). Moreover, some indication of a similar effect was present in an objective measure of speech-related functioning (verbal fluency), but this effect is much less clear in the data and requires careful consideration. Of note, the speech-functioning scores (PROM and objective) themselves did not correlate with each other within this subgroup. The larynx subgroup was also the group showing an effect of alcohol consumption with respect to PROM-speech, but rather in the opposite direction: the group with no current (or past) excessive alcohol consumption experienced more PROM-speech problems. Possibly, individuals with speech problems may have been more likely to stop drinking, while those with few speech problems were less dissuaded from excessive consumption. It is also possible that individuals with excessive alcohol intake tend to avoid social situations with conversations more than those without excessive intake, and therefore are less confronted with or aware of their speech problems. However, these explanations are speculative and future studies should look into this issue more carefully before conclusions can be drawn.

We also found a relationship between the patient-reported outcome measures of speech and perceived neurocognitive functioning for the larynx and oropharynx subgroups, but not for the oral cavity, hypopharynx, and unknown primary subgroups. This consistent, but modest, association between perceived neurocognitive and speech problems indicates that those patients who report more speech problems also experience more problems in attention, memory, and so on, which however do not appear to be related to their actual neurocognitive performance level. Previous studies have also found clusters of patient-reported outcome measures in patient samples with HNC, in the absence of correlations with objective neurocognitive measures.[10,11] Interestingly, the larynx subgroup was the group showing the strongest relationship between the PROMs (from the linear, parametric correlations and the monotonic, nonparametric correlations; see Supporting Information). It would be important for future studies to investigate whether the larynx group is particularly susceptible to

treatment-related problems in neurocognitive functioning, in addition to the speech domain.

Given the issue of partly overlapping samples with our previous study on a smaller sample,[8] we lowered the alpha level of all analyses reported here to control for the increased risk of false positive in the context of sequential analyses.[19] Strictly speaking, we lowered the alpha level beyond what would have been required (to 0.01 instead of 0.025, assuming an initial alpha level of 0.05 and the present study representing the second "re-analysis" of the data). Although this stricter threshold may have increased the risk of false negatives, we can be more confident about the positive findings and remain cautious about interpreting the absence of effects, especially if absent effects are not further supported by previous literature.

An important consideration for our results is the fact that the data were obtained before the start of treatment but after the patients had received their diagnoses. A diagnosis of cancer is associated with distress[38] and this, in turn, may have contributed to worsening of neurocognitive and speech functioning, both self-reported and objectively measured.[34] However, the fact that the group with larynx tumors showed a tendency to worse functioning in activities requiring speech from the self-reported measure, and possibly also, albeit much more weakly, from the objective measure, could indicate that not all of the pretreatment deficits are easily explained by postdiagnosis distress.

Our study is limited by the fact that our design did not include other reference groups with or without cancer, so we do not know how specific our results are to HNC, and the estimated prevalence of neurocognitive impairment may be somewhat overestimated, as discussed above.[34] Moreover, our inferences are shaped by the instruments we used, including the specific neuropsychological tests we selected and the use of self-report measures of tobacco and alcohol use. For example, the negative effects of chronic tobacco and alcohol use on brain health and cognition are clear,[15–18] but the use of self-reported measures of intake may add a level of complexity to this issue. Additionally, the use of the Speech Handicap Index does not permit us to make inferences about language functioning or word finding in this population. Another limitation relates to the generalizability of our findings, given that the NET-QUBIC cohort was not fully representative for the Dutch population of HNC with respect to age, sex, and tumor subsite (specific details are provided in the protocol report of the NET-QUBIC study).[13] We also had a high level of missing data for the speech and neurocognitive assessments, which is a limiting factor in our study. Additionally, comorbidity and performance status, potentially important covariates, were not addressed in the present study. Finally, the effect of tumor subsite on verbal fluency, and in particular for the larynx subgroup, was found but the overall regression model had poor explanatory power. This issue requires consideration and future studies are needed to further confirm this finding based on the a priori hypotheses established by our study.

In line with the future directions pointed out above, our study stresses the need for large multicenter (across countries and cultures) and longitudinal cohort studies, with a control group without a cancer diagnosis as well as with groups of patients with other cancer types, including detailed assessment of speech and objective neurocognitive performance (in addition to PROMs). Regarding the group with larynx tumors, future studies could examine whether this group is particularly susceptible to treatment-related problems in the domains of speech and neurocognition, given the tentative suggestion from our data that this group may have a somewhat accentuated level of deficit in speech(-related) functioning. If motor speech and voice quality improve in this group after treatment, but neurocognitive tasks involving speech production do not, one may be better able to disentangle these two important domains—speech and neurocognition—in the population with HNC.

5 | CONCLUSION

In conclusion, using the largest sample of patients with HNC before treatment to date, we found that a relatively large subgroup of patients with HNC reports perceived deficits in speech functioning, which tends to be larger in the larynx group. A small subgroup presents with deficits in neurocognitive functioning (from self-report and objective measures), possibly accentuated in the case of larynx tumors. Future studies could examine whether the larynx cancer group is particularly susceptible to treatment-related problems in the domains of speech and neurocognition.

ACKNOWLEDGMENT

This work was supported by the Dutch Cancer Society (KWF-Alpe d'Huzes, to NET-QUBIC Consortium).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ETHICS STATEMENT

The study protocol has been approved by the Institutional Review Board of the coordinating research center (Amsterdam UMC [location VUmc]) (2013.301

(A2018.307)-NL45051.029.13). Participants provided written informed consent that their data and samples be used and re-used in future studies related to health-related quality of life in head and neck cancer. The NET-QUBIC Research Agreement is signed by all participating hospitals.

DATA AVAILABILITY STATEMENT

Data and materials are described on the NET-QUBIC project website (www.kubusproject.nl). The collection and integration of large amounts of personal, biological, genetic, and diagnostic information precludes open access to the NET-QUBIC research data. In the section Data and sample dissemination, it is described how the data are made available for the research community.

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How to cite this article: Piai V, Jansen F, Dahlslätt K, et al. Prevalence of neurocognitive and perceived speech deficits in patients with head and neck cancer before treatment: Associations with demographic, behavioral, and disease-related factors. *Head & Neck*. 2022;44(2):332-344. doi:10.1002/hed.26930