

## Original Article

# The effect of body mass index at diagnosis on survival of patients with squamous cell head and neck carcinoma

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**Abstract:** The aim of this study is to investigate the prognostic role of body mass index (BMI) on survival from head and neck cancer (HNC). We performed a pooled analysis of studies included in the International Head and Neck Cancer Epidemiology consortium. We used Cox proportional hazards models to estimate the adjusted hazard ratios (HR) for overall survival and HNC-specific survival, and we stratified the results according to cancer site. The study included 10,177 patients from 10 studies worldwide. Underweight patients had lower overall survival (HR=1.69, 95% CI: 1.31-2.19) respect to those having normal weight with consistent results across the HNC sites. Overweight and obese patients had a favourable HNC-specific survival (HR=0.77 (95% CI: 0.70-0.84) and HR=0.80 (95% CI: 0.76-0.84), respectively), with heterogenous results according to HNC site. Our findings show that high BMI values

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at cancer diagnosis improved the survival rates in patients with HNC, especially among smokers. This association may be explained by residual confounding, reverse causation, and collider stratification bias, but may also suggest that a nutritional reserve may help patients survive HNC cancer.

**Keywords:** Body mass index, head and neck cancer, survival

## Introduction

Head and neck cancers (HNCs) represent the sixth most common cancer worldwide, with approximately 330,000 deaths globally each year [1]. The overall survival (OS) and HNC-specific survival vary and depend on several factors. Aside from cancer stage and Human Papillomavirus (HPV) infection, other predictors appear to be tobacco smoking [2, 3], comorbidities [4], physical activity, and socio-economic status [2-8]. Nutritional status is another important factor since the percentage of people with advanced HNC who present malnutrition goes from 42% to 77% as a consequence of chewing and swallowing problems secondary to the disease itself or to cancer cachexia [9, 10].

Body mass index (BMI), an indicator of nutritional status and total body fat, has been found to be positively associated with the incidence of several chronic diseases, particularly cardiovascular diseases and several cancers [11], including HNC [12-14]. In addition, various studies suggest that obesity and being overweight may increase cancer mortality [12, 15-20]. Despite the evidence that excess mortality increases with increasing BMI, some studies concluded that elevated BMI may improve survival in patients with several chronic diseases, a phenomenon called the obesity paradox. Different mechanisms have been postulated to support the existence of this paradox [21], suggesting that increased body weight may hinder the metabolic consequences of diseases and of treatments by providing adequate muscle and adipose reserves, thus prolonging survival [22, 23]. There is growing evidence, however, that this pattern of association could also be explained by methodological flaws, namely collider stratification bias (where subject selection is influenced by BMI and an unmeasured risk factor for mortality) [24, 25], unmeasured confounders (e.g., smoking), reverse causation (where BMI increases the risk of serious illness but that illness also reduces BMI before dying) [12, 20, 26-35], and bias due to limitations of BMI for measuring obesity (since BMI may reflect unmeasured differences in body composition, muscle mass, and weight change) [33].

A large cohort study, addressing some of these methodological issues, reported that the occurrence of the obesity paradox might change according to cancer site [12]. To date, with regards to HNC patients, the evidence is controversial as it comes from a limited number of studies, mainly with small sample sizes [36].

In this study, we evaluated the prognostic role of BMI at diagnosis and survival in HNC by performing a pooled analysis of cohort studies included in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.

## Materials and methods

### *Study population*

In this pooled analysis within the INHANCE consortium [13], we included data provided by independent survival studies, as follows: Italy study (Rome [37], Milan [38], and Aviano, Padua and Turin, three centers of the European ARCADE study [39]), Central Europe study (Poland and Hungary) [40], HN5000 study (UK) [41], Boston study [42], Los Angeles study [43], Michigan study [44], North Carolina study (USA) [45], Toronto study - MSH-PMH/Mount Sinai Hospital - Princess Margaret Hospital (Canada) [46], Buenos Aires study (Argentina) [47] and São Paulo study (Brazil) [48] ([Supplementary Table 1](#)). Cases were patients aged  $\geq 18$  years with histologically confirmed cancers of the oral cavity, oropharynx, hypopharynx and larynx. Written informed consent was obtained from all study subjects and the studies were approved by relevant ethics committees at each of the institutes involved [5].

### *Data collection*

Questionnaires were collected from all of the individual studies, to assess the comparability of the collected data and of the wording of interview questions among the studies. Data from individual studies were received with personal identifiers removed. Each data item was checked for illogical or missing values and inconsistencies were resolved as necessary. Demographic, lifestyle and clinical information

was obtained. These data were previously pooled and managed by the INHANCE consortium coordination [5]. All cases were followed from the date of diagnosis to the date of death or the end of follow-up, whichever occurred first. The cause of death was obtained from the death certificate data and coded according to the International Classification of Diseases, Tenth Revision (ICD-10). All follow-up information was shared by each study coordinator with the coordinating center at the Università Cattolica del Sacro Cuore in Rome, Italy. All data were harmonized and checked for internal consistency. Clarifications were requested from the original investigators if required.

### *Variables and outcome definition*

HNCs were classified according to the following anatomic sites using the ICD-10 codes: oral cavity (C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8, and C06.9), oropharynx (C01, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2-C10.4, C10.8, and C10.9), hypopharynx (C12.9, C13.0-C13.2, C13.8, and C13.9), larynx (C10.1, C32.0-C32.3, and C32.8-C32.9) [13]. Information on height and weight was recorded at the time of diagnosis. BMI was calculated as the weight divided by the height squared (weight (kg)/height (m)<sup>2</sup>) and categorized into four groups according to the World Health Organization (WHO) categories: underweight <18.5; normal weight 18.5-24.9; overweight 25.0-29.9; obese ≥30.0 [49]. Cancers were staged according to the TNM Staging System, 7<sup>th</sup> edition [50] and categorized as early (stage I and II) and advanced (stage III and IV) stages.

Smoking status was categorized as never, current, and former smokers or missing in case the information was not available. Former users were defined as those who quit cigarette smoking for 1 or more years prior to the cancer diagnosis.

The frequency of tobacco consumption was assessed as never smokers, ≤20 cigarettes/day, or >20 cigarettes/day. Smoking duration was categorized as never smokers, ≤20 years, or >20 years. Additionally, pack-years, calculated as twenty cigarettes smoked every day for one year, were determined.

Drinking status was categorized as never-drinkers, ever-drinkers, or missing when the information was not available. For alcohol consumption, subjects were classified as none, ≤1 drink equivalent/day, or >1 drink equivalent/day. Regarding alcohol duration, categories included never, ≤20 years, and >20 years. To calculate the quantity of alcohol consumed, the number of drinks (15.6 ml of ethanol) per day was multiplied by the duration in years.

Treatment was clustered into five categories: none, surgery only, surgery and radiation, radiation and/or chemotherapy, and surgery and chemotherapy (with or without radiation).

Education level was categorized in six categories (“No education”, “≤ Junior high school”, “Some high school”, “High school graduate”, “Technical school, some college”, “≥ College graduate”).

### *Statistical analysis*

Descriptive statistics were conducted to describe the study participants. Categorical variables were expressed as absolute frequencies and percentages; continuous variables were expressed as median and interquartile range (IQR).

The overall survival was defined as the time from the date of HNC diagnosis until death due to any cause. The HNC-specific survival was defined as the time from the date of HNC diagnosis to the date of death from HNC. Patients not known to have died at the time of analysis were censored based on the last recorded date on which they were known to be alive. We used the Kaplan-Meier method to calculate the cumulative proportion surviving by BMI categories and to plot the unadjusted overall 5-year survival curves.

Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the overall and HNC-specific survival. The impact of predictor variables on overall and HNC-specific survival was determined using crude and adjusted analyses. In the initial crude analyses, epidemiological variables included age in years, gender, education, and smoking and alcohol status, while clinical characteristics included tumour site and stage. A multivariable proportional hazards model was

set up by including the variables that reported a prognostic potential in the univariate analysis ( $P < 0.1$ ). Furthermore, in order to account for different treatment access and types, the multivariable models were adjusted also by region of study centre (Europe, North America, South America). We used Schoenfeld residuals to formally test the Cox proportional hazards assumption for each covariate [51]. The BMI category “normal weight” was set as the reference category. We performed a test for linear trend to evaluate a relationship dose-response of the effect of the BMI on the outcome.

Since the information about education level was missing for 3184 cases, we applied multiple imputations (five imputations) with the MI impute procedure in Stata. We assumed that the education data were missing at random (i.e., whether education was missing or not did not depend on any other unobserved or missing values). We used the logistic regression model to predict education level with age at diagnosis, gender, study centre within each region separately, as previously done in other INHANCE studies [52]. The logistic regression results to assess summary estimates for BMI for five imputations were combined by using the MI estimate procedure in Stata statistical software. We compared the results with the complete case analysis to assess the influence of the imputation on the observed association.

We conducted a sensitivity analysis to examine the relationship between prognosis and body mass index, while considering the type of cancer treatment, as well as the duration and intensity of smoking and alcohol use. Due to the partial availability of data on these variables within the consortium, the analysis was performed in a smaller subset of centers.

In order to evaluate the potential effect modification of smoking, one of the major predictors of HNC survival [2], on the relationship between BMI at diagnosis and survival, we conducted the analyses on never- and ever-smokers, separately. The analyses among ever-smokers were additionally adjusted for pack-years smoking.

Furthermore, a one-stage meta-analysis was conducted using a Cox proportional hazard mixed-effects model with a random intercept for region (following the Gamma distribution). This analysis aimed to assess the association

between BMI and overall survival, as well as site-specific survival for HNC. Stratification was performed based on HNC site, and additional analyses were conducted considering smoking habits.

Finally, to evaluate the possibility of reverse causation, sensitivity analyses on the relationship between BMI at diagnosis and OS/HNC-specific survival were conducted including patients whose follow-up period was longer than 5 years. All statistical analyses were performed using Stata software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP) and R version 4.2.0 (2022-04-22) for Windows.

### Results

Among 10,177 patients ([Supplementary Figure 1](#)), the most common categories were males (77.8%), ever-drinkers (83.2%), former smokers (40.4%), and within a normal weight BMI category (42.1%). **Table 1** reports patient's characteristics overall and by HNC site. Except for laryngeal cancer, the majority of patients with cancers at other HNC sites were recorded as having an advanced tumour stage (stage III-IV). Laryngeal cancer patients have a higher median age at diagnosis (63 years; IQR=56-70) and increased pack-years smoking intensity (median of 40 pack-years; IQR=23-60), compared to other HNC sites ( $P < 0.0001$ ). Demographic, clinical, and behavioural characteristics distribution according to each participating INHANCE study are reported in [Supplementary Table 2](#).

During a median follow-up time of 48 months, 3654 all-cause and 1202 HNC-specific deaths were observed. **Figure 1** shows the overall survival by BMI categories for each HNC site. Crude (unadjusted) survival analyses revealed appreciable differences in overall survival among the BMI categories (log-rank test,  $P < 0.0001$ ). The 5-year overall survival rates for oral cavity cancer patients were: 39% (95% CI: 31%-48%) for underweight, 56% (95% CI: 53%-59%) for normal weight, 64% (95% CI: 60%-67%) for overweight, and 66% (95% CI: 62%-71%) for obese. In oropharyngeal cancer patients the 5-year overall survival rates were 34% (95% CI: 26%-42%), 65% (95% CI: 63%-68%), 76% (95% CI: 74%-79%) and 79% (95% CI: 76%-82%), respectively. For patients with hypopharyngeal cancer, the 5-year survival rates were 18% (95% CI:

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**Table 1.** Demographic, clinical, and behavioural characteristics of 10,177 HNC patients from the 10 studies within INHANCE consortium, according to HNC site

		Oral Cavity (N=3120)		Oropharynx (N=3844)		Hypopharynx (N=550)		Larynx (N=2663)		Total (N=10,177)	
		n	%	n	%	n	%	n	%	n	%
Gender											
	Female	1049	33.7	714	18.6	89	16.2	402	15.1	2254	22.2
	Male	2064	66.3	3129	81.4	461	83.8	2258	84.9	7912	77.8
	Missing	7	0.2	1	0.03	0	0.0	3	0.1	11	0.1
Age at diagnosis (yrs), median (IQR)		61 (53-70)		58 (52-65)		60 (54-68)		63 (56-70)		60 (53-68)	
Region Study											
Europe	Italy	92	2.9	82	2.1	28	5.1	140	5.3	342	3.3
	Central Europe	72	2.3	77	2.0	9	1.6	39	1.4	197	1.9
	UK	836	26.8	1294	33.7	149	27.1	720	27.0	2999	29.5
North America	Boston	199	6.4	423	11.0	46	8.4	132	5.0	800	7.9
	Los Angeles	48	1.5	141	3.7	15	2.7	80	3.0	284	2.8
	Michigan	365	11.7	350	9.1	30	5.5	173	6.5	918	9.0
	North Carolina	183	5.9	359	9.3	60	10.9	465	17.5	1067	10.5
	Toronto	618	19.8	794	20.7	72	13.1	396	14.9	1880	18.5
South America	Buenos Aires	18	0.6	17	0.4	3	0.5	32	1.2	70	0.7
	São Paulo	689	22.1	307	8.0	138	25.1	486	18.2	1620	15.9
BMI categories											
	Underweight	160	5.1	166	4.3	58	10.5	117	4.4	501	4.9
	Normal weight	1458	46.7	1464	38.1	298	54.2	1064	39.9	4284	42.1
	Overweight	988	31.7	1373	35.7	134	24.4	963	36.2	3458	34.0
	Obese	514	16.5	841	21.9	60	10.9	519	19.5	1934	19.0
Education level											
	No education	64	3.1	22	0.8	13	3.1	53	2.7	152	2.2
	≤ Junior high school	497	24.3	273	10.6	106	24.8	407	20.9	1283	18.4
	Some high school	630	30.8	801	31.2	143	33.5	683	35.0	2257	32.3
	High school graduate	306	14.9	466	18.2	65	15.2	348	17.8	1185	16.9
	Technical school, some college	240	11.7	466	18.2	50	11.7	268	13.7	1024	14.6
	≥ College graduate	311	15.2	538	21.0	50	11.7	193	9.9	1092	15.6
	Missing	1072	34.4	1278	33.3	123	22.4	711	26.7	3184	31.3
Tumour stage											
	I-II	1410	45.2	572	14.9	81	14.7	1380	51.8	3443	33.8
	III-IV	1710	54.8	3272	85.1	469	85.3	1283	48.2	6734	66.2

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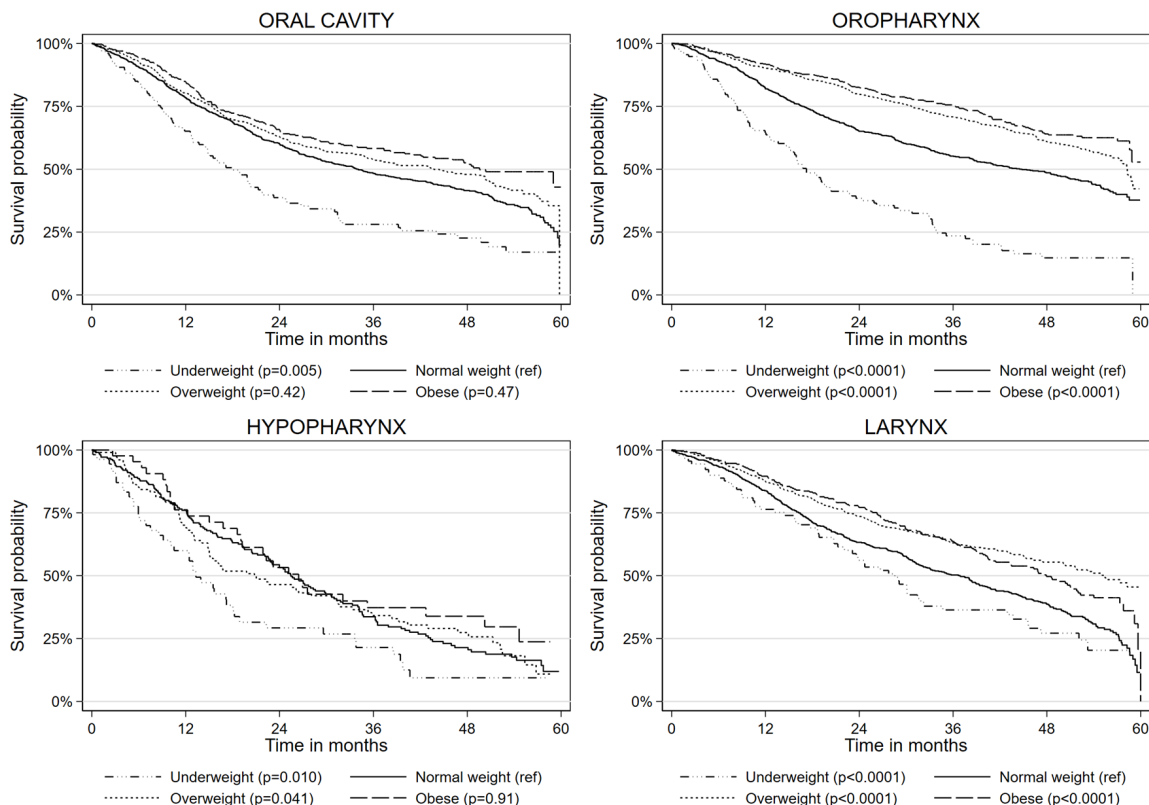
Cigarette smoking										
Smoking status										
Never	726	24.0	975	26.3	42	7.9	237	9.2	1980	20.1
Former	1060	35.1	1559	42.0	195	36.7	1162	44.9	3976	40.4
Current	1238	40.9	1175	31.7	294	55.4	1188	45.9	3895	39.5
Missing	96	3.1	135	3.5	19	3.4	76	2.9	326	3.2
Years of smoking										
Never smokers	726	29.8	975	30.7	42	9.4	237	11.1	1980	24.2
≤20	299	12.2	602	19.0	38	8.5	218	10.2	1157	14.1
>20	1415	58.0	1594	50.3	366	82.1	1682	78.7	5057	61.7
Missing	680	21.8	673	17.5	104	18.9	526	19.7	1983	19.5
Cigarettes per day										
Never smokers	726	30.3	975	31.1	42	10.1	237	11.3	1980	24.6
≤20	1147	48.0	1520	48.5	244	58.8	1147	54.8	4058	50.5
>20	519	21.7	638	20.4	129	31.1	711	33.9	1997	24.9
Missing	728	23.3	711	18.5	135	24.5	568	21.3	2142	21.1
Pack-year for ever smokers, <i>median (IQR)</i>	33 (17-50)		28 (12-45)		38 (24-53)		40 (24-60)		34 (18-51)	
Alcohol drinking										
Drinking status										
Never	597	20.8	541	15.1	55	10.6	400	16.0	1593	16.8
Ever	2279	79.2	3031	84.9	464	89.4	2100	84.0	7874	83.2
Missing	244	7.8	272	7.1	31	5.6	163	6.1	710	7.0
Years of alcohol consumption										
Never drinkers	143	13.4	104	8.3	11	4.4	140	11.8	398	10.6
≤20	83	7.8	149	11.9	28	11.3	108	9.1	368	9.8
>20	839	78.8	1002	79.8	209	84.3	938	79.1	2988	79.6
Missing	2055	65.9	2589	67.4	302	54.9	1477	55.5	6423	63.1
Drinks per day										
Never drinkers	597	27.3	541	20.5	55	13.3	400	19.8	1593	22.0
≤1	564	25.8	747	28.4	80	19.4	511	25.3	1902	26.2
>1	1028	46.9	1344	51.1	278	67.3	1111	54.9	3761	51.8
Missing	931	29.8	1212	31.5	137	24.9	641	24.1	2921	28.7
Drink/day per year for ever-drinkers, <i>median (IQR)</i>	135 (37-340)		86 (26-209)		187 (85-342)		140 (47-304)		122 (37-279)	
Treatment										
No	103	3.5	54	1.6	24	5.0	29	1.2	210	2.3
Surgery only	1290	44.5	196	5.6	43	8.9	434	18.0	1963	21.2

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Surgery and radiation	816	28.2	358	10.3	78	16.2	406	16.9	1658	17.9
Radiation and/or chemotherapy	318	11.0	2512	72.1	285	59.3	1401	58.2	4516	48.7
Surgery and chemo ± radiation*	370	12.8	364	10.4	51	10.6	137	5.7	922	9.9
Missing	223	7.2	360	9.4	69	12.6	256	9.6	908	8.9
Follow-up (months), median (IQR)	42 (16-63)		51 (26-70)		30 (12-61)		51 (24-73)		48 (20-69)	
Status										
Alive	1878	60.2	2726	70.9	221	40.2	1698	63.8	6523	64.1
Dead	1242	39.8	1118	29.1	329	59.8	965	36.2	3654	35.9
Deaths from HNC	466/1242	37.5	319/1118	28.5	122/329	37.1	295/965	30.6	1202/3654	32.9

Abbreviations: HNC = head and neck cancer, IQR = interquartile range, BMI = body mass index. \*Surgery and chemotherapy (with or without radiation).

## BMI and head and neck cancer survival



**Figure 1.** Overall survival among HNC sites, by BMI categories.

8%-30%), 45% (95% CI: 39%-51%), 40% (95% CI: 31%-49%) and 50% (95% CI: 36%-62%); in patients with laryngeal cancer, they were 44% (95% CI: 34%-55%), 58% (95% CI: 55%-62%), 75% (95% CI: 72%-78%) and 71% (95% CI: 66%-75%).

Adjusted associations of BMI categories with overall and HNC-specific survival are reported in **Table 2** (crude associations are reported in **Supplementary Table 3**).

In the overall survival analyses (upper panel of **Table 2** and **Supplementary Table 3**), underweight patients had a lower overall survival across all HNC sites in both adjusted (HR=1.69, 95% CI: 1.31-2.19) and unadjusted models (HR=2.00, 95% CI: 1.80-2.22) than normal-weight patients. The adjusted overall survival was greatest for patients with hypopharyngeal cancer (HR=2.00, 95% CI: 1.18-3.39) and smallest for patients with laryngeal cancer (HR=1.49, 95% CI: 1.25-1.78). In contrast, overweight and obese patients across all HNC sites had lower adjusted HRs of 0.77 (95% CI:

0.70-0.84) and 0.76 (95% CI: 0.64-0.90), respectively.

In HNC-specific mortality analyses (lower panel of **Table 2** and **Supplementary Table 4**), the survival for underweight patients was not significantly decreased, except for those with oropharyngeal cancer (HR=1.43, 95% CI: 1.11-1.83). Overweight and obese patients for all HNC sites had favourable adjusted HRs of 0.77 (95% CI: 0.70-0.84) and 0.80 (95% CI: 0.76-0.84), respectively.

In the HNC subsite analysis, the protective effect was confirmed only for oropharyngeal cancers (HR=0.50 (95% CI: 0.33-0.75) and HR=0.51 (95% CI: 0.36-0.72)). The pattern of findings was similar for the analysis without imputed data.

The favourable prognosis for overweight patients is further supported by a sensitivity analysis conducted on 2828 patients, which adjusted for treatment, intensity and duration of smoking, and alcohol consumption (**Supplementary Table 5**).



## BMI and head and neck cancer survival

**Table 2.** Adjusted analysis\* for the association between BMI and overall and HNC-specific survival, by HNC site

	Oral Cavity			Oropharynx			Hypopharynx			Larynx			All HNC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Overall survival	(N=2573)			(N=3322)			(N=463)			(N=2309)			(N=8667)		
Underweight	1.56	1.14-2.14	0.005	1.94	1.34-2.81	<0.0001	2.00	1.18-3.39	0.010	1.49	1.25-1.78	<0.0001	1.69	1.31-2.19	<0.0001
Normal weight	1			1			1			1			1		
Overweight	0.95	0.82-1.08	0.42	0.69	0.58-0.81	<0.0001	1.25	1.01-1.55	0.041	0.70	0.61-0.81	<0.0001	0.77	0.70-0.84	<0.0001
Obese	0.88	0.62-1.25	0.47	0.67	0.60-0.75	<0.0001	0.96	0.47-1.98	0.91	0.82	0.77-0.88	<0.0001	0.76	0.64-0.90	0.001
HNC-specific survival	(N=2573)			(N=3322)			(N=463)			(N=2309)			(N=8667)		
Underweight	1.27	0.48-3.33	0.63	1.43	1.11-1.83	0.006	1.88	0.33-10.76	0.48	1.01	0.83-1.24	0.90	1.33	0.77-2.30	0.30
Normal weight	1			1			1			1			1		
Overweight	1.09	0.88-1.34	0.43	0.50	0.33-0.75	0.001	1.31	0.97-1.78	0.08	0.75	0.68-0.82	<0.0001	0.77	0.70-0.84	<0.0001
Obese	1.07	0.85-1.35	0.55	0.51	0.36-0.72	<0.0001	1.34	0.47-3.77	0.58	0.98	0.61-1.56	0.93	0.80	0.76-0.84	<0.0001

\*For age at diagnosis, gender, tumour stage, education level, smoking status, drinking status and region. Reference: normal weight. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval.

**Table 3A** and **3B** report the results of the survival analysis according to smoking status. Among ever-smokers, overweight and obese categories of BMI showed a favourable overall and HNC-specific survival, while underweight had an unfavourable survival in the overall survival analysis.

Underweight is associated with a lower overall survival and HNC-specific survival for patients with cancer of oropharynx (HR=1.72, 95% CI: 1.21-2.44; HR=1.60, 95% CI: 1.20-2.13); overweight and obese categories are associated with a higher overall survival and HNC-specific survival for patients with cancer of oropharynx (HR=0.63, 95% CI: 0.47-0.83; HR=0.42, 95% CI: 0.21-0.84) (HR=0.59, 95% CI: 0.50-0.69; HR=0.53, 95% CI: 0.34-0.83) (**Table 3A** and **3B**).

Among never-smokers, BMI status was not associated with overall and HNC-specific survival, however the sample size was too small to conclude whether there is an actual heterogeneity (**Table 3A** and **3B**). These findings remained consistent when using a one-stage Cox proportional hazard mixed-effects model ([Supplementary Tables 6, 7A](#) and [7B](#)).

When the analysis on overall survival and HNC-specific survival was restricted to patients with a follow-up longer than 5 years, 417 all-cause and 87 HNC-specific deaths were observed. Survival analysis shows a higher survival for overweight patients (HR=0.90, 95% CI: 0.84-0.97) only in the overall survival analysis. BMI status was not associated with overall and HNC specific survival in never-smokers and ever-smokers separately (data not shown).

### Discussion

Our analysis reports the results of the largest available pooled analysis on the prognostic significance of BMI on the survival of 10,177 HNC patients from 10 studies worldwide. After adjusting for major confounders, the underweight category of BMI is associated with lower overall survival. The results were consistent for all HNC sites. In contrast, high BMI values are associated with higher overall survival in oropharyngeal and larynx cancer. In HNC-specific mortality analyses, the overall survival for underweight was significantly unfavourable for patients with oropharyngeal cancer. Moreover,

overweight and obese patients for oropharyngeal cancers had a favourable survival.

The positive association between BMI and survival in HNCs is consistent with evidence provided by previous single-center studies [20, 36, 44, 53, 54], which reported that overweight at diagnosis was associated with higher survival compared with other BMI categories. In a cohort of 1,059,153 patients, by Gaudet et al., the categories of BMI 25.0-29.9 and  $\geq 30.0$  kg/m<sup>2</sup> (compared with the category of BMI 22.5-24.9) were associated with a lower risk of HNC mortality but not incidence, whereas when stratifying by smoking status, they observed an association of underweight with a higher risk of HNC mortality only in smokers [55].

Few studies have attempted to address this association with subgroup analysis by HNC site. Regarding oral cancers, our results were consistent with previous cohort studies [56]. A retrospective cohort study in China [56], reported that, in 633 patients undergoing surgery, BMI was not associated with differences in HNC-specific survival, whereas obese patients had higher risks of recurrence. In our analysis, lower overall survival was observed in underweight patients for all HNC sites and a lower HNC-specific survival was observed in patients with oropharyngeal cancer, which might be due to the fact that these patients are at high risk of malnutrition because of chewing and swallowing problems secondary to the disease or treatment [9, 57]. As a consequence, it might support the hypothesis that adiposity could serve as a nutrient reserve or that high BMI is less frequently associated to sarcopenia which is a major prognostic factor [23, 58].

Stratified analysis according to smoking status show that underweight patients with oropharynx cancer experienced a lower overall survival and HNC specific survival, especially among ever-smokers.

There is a well-known association between HNC risk and smoking habits, as well as between BMI and HNCs [12, 14, 35]. Furthermore, according to the literature, individuals with low BMI are more prone to smoking compared to individuals with high BMI [59-61]. As a result of that, the obesity paradox in ever-smokers (e.g., favourable survival among overweight and obese) could be partially or fully

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**Table 3A.** Adjusted analysis\* for the association between BMI and overall survival by HNC site and according to smoking habits

	Oral Cavity			Oropharynx			Hypopharynx			Larynx			All HNC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Never-smokers	(N=619)			(N=884)			(N=38)			(N=212)			(N=1753)		
Underweight	1.58	0.58-4.26	0.37	3.26	0.42-25.37	0.26	-	-	-	0.42	0.07-2.50	0.34	1.50	0.33-6.72	0.60
Normal weight	1			1			1			1			1		
Overweight	0.93	0.73-1.17	0.53	0.98	0.69-1.40	0.91	2.33	0.22-24.41	0.48	0.80	0.50-1.30	0.37	0.86	0.67-1.12	0.26
Obese	1.04	0.57-1.91	0.89	0.99	0.74-1.32	0.92	1.96	0.61-6.27	0.26	0.85	0.43-1.65	0.63	0.94	0.66-1.34	0.73
Ever-smokers**	(N=1389)			(N=1767)			(N=320)			(N=1592)			(N=5068)		
Underweight	1.41	1.31-1.52	<0.0001	1.72	1.21-2.44	0.003	1.97	0.91-4.27	0.08	1.57	1.32-1.87	<0.0001	1.61	1.31-1.98	<0.0001
Normal weight	1			1			1			1			1		
Overweight	0.98	0.73-1.31	0.89	0.63	0.47-0.83	0.001	1.38	1.09-1.75	0.007	0.68	0.56-0.82	<0.0001	0.74	0.65-0.85	<0.0001
Obese	0.80	0.61-1.05	0.10	0.59	0.50-0.69	<0.0001	1.03	0.51-2.09	0.94	0.79	0.71-0.87	<0.0001	0.70	0.63-0.77	<0.0001

\*For age at diagnosis, gender, tumour stage, education level, smoking status, drinking status and region. Reference: normal weight. \*\*Also adjusted for pack-years smoking. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval. - HR and CI not estimated for low sample size.

**Table 3B.** Adjusted analysis\* for the association between BMI and HNC-specific survival by HNC site and according to smoking habits

	Oral Cavity			Oropharynx			Hypopharynx			Larynx			All HNC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Never-smokers	(N=619)			(N=884)			(N=38)			(N=212)			(N=1753)		
Underweight	0.52	0.37-0.72	<0.0001	1.41	0.04-49.31	0.85	-	-	-	-	-	-	0.55	0.07-4.61	0.58
Normal weight	1			1			1			1			1		
Overweight	1.18	0.77-1.82	0.44	0.75	0.34-1.68	0.49	0.82	0.13-5.34	0.84	0.69	0.38-1.26	0.23	0.85	0.52-1.38	0.50
Obese	2.07	1.31-3.26	0.002	0.40	0.21-0.76	0.006	0.50	0.01-19.97	0.71	1.88	0.88-3.99	0.10	1.04	0.68-1.60	0.84
Ever-smokers**	(N=1389)			(N=1767)			(N=320)			(N=1592)			(N=5068)		
Underweight	1.38	0.57-3.36	0.47	1.60	1.20-2.13	0.001	1.68	0.28-10.11	0.57	1.23	0.98-1.53	0.07	1.46	0.89-2.41	0.14
Normal weight	1			1			1			1			1		
Overweight	1.10	0.87-1.39	0.42	0.42	0.21-0.84	0.014	1.22	0.82-1.80	0.33	0.69	0.61-0.77	<0.0001	0.69	0.56-0.86	0.001
Obese	0.81	0.69-0.94	0.005	0.53	0.34-0.83	0.005	1.39	0.52-3.74	0.51	0.83	0.56-1.23	0.35	0.70	0.61-0.80	<0.0001

\*For age at diagnosis, gender, tumour stage, education level, smoking status, drinking status and region. Reference: normal weight. \*\*Also adjusted for pack-years smoking. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval. - HR and CI not estimated for low sample size.

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explained by some methodological issues such as residual confounding due to inadequate statistical adjustment, collider bias (which occurs when common causes of HNC (here, elevated BMI and smoking) affect inclusion into the analysis), and reverse causality (since smokers could be at higher risk of death). When the analysis on HNC-specific survival was restricted to patients with a follow-up greater than 5 years, BMI status was not associated with HNC specific survival, neither overall nor separately in never- and ever-smokers (despite the low sample size).

To our knowledge, this study represents one of the largest survival analyses on the association between BMI and HNCs. Other strengths include available information on potential confounders, including education level, drinking, and smoking status and pack-years which are closely related to BMI. We acknowledge however that our study has several limitations. First, BMI is an imperfect proxy of body fat not providing information on fat distribution and muscle mass which may impact cancer survival. Other measures, such as waist circumference and central adiposity were not available. BMI however is acknowledged as the most relevant and popular index for assessing nutritional status in adults [62]. Second, the data were analysed based on the BMI at diagnosis, and it was not possible to evaluate to which degree the BMI prior to diagnosis or the BMI after treatment might have changed the results. Similarly, for smoking status, the self-reported information was not collected during the follow-up for any changes on smoking habits. Moreover, we lacked data on patients' behaviour post-diagnosis, which could have influenced overall and specific survival outcomes. Additionally, we acknowledge other limitations, such as the different selection criteria used by the studies, response rate at recruitment, treatment approaches for different HNC sites and the unavailability of specific data on the treatments like potential targeted therapy and biochemical or laboratory indicators. Moreover, residual confounding might be expected since we were not able to account for comorbidities, presence of metastasis and HPV status for oropharyngeal cancer.

Future research should aim to investigate better the relation between BMI, overall survival and HNC-specific survival, in particular for HNC

sites, by prospectively collecting data on BMI and the changes over time, and by including data on muscle mass, fat distribution and other relevant confounders, such as co-morbidities, HPV, or treatment approaches.

### Conclusions

This study provides further evidence on the potential role of BMI at diagnosis in HNC survival, reporting that high BMI values are associated with favourable survival estimates, during a median follow-up period of 48 months. The estimates varied across HNC sites and smoking status. BMI at diagnosis could serve as a potential prognostic factor, however, there is the need to further investigate its role through predictive models, which consider trends of BMI after the diagnosis. Further studies should better investigate the role of this composite proxy of nutritional status since, albeit imperfect, it still represents one of the most easy-to-collect and readily available measures of body fat used in clinical practice.

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### Disclosure of conflict of interest

None.

## Abbreviations

BMI, body mass index; CI, confidence interval; HNC, head and neck cancer; HPV, Human Papillomavirus infection; HR, hazard ratios; INHANCE, International Head and Neck Cancer Epidemiology consortium; IQR, interquartile range; OS, overall survival; WHO, World Health Organization.

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## BMI and head and neck cancer survival

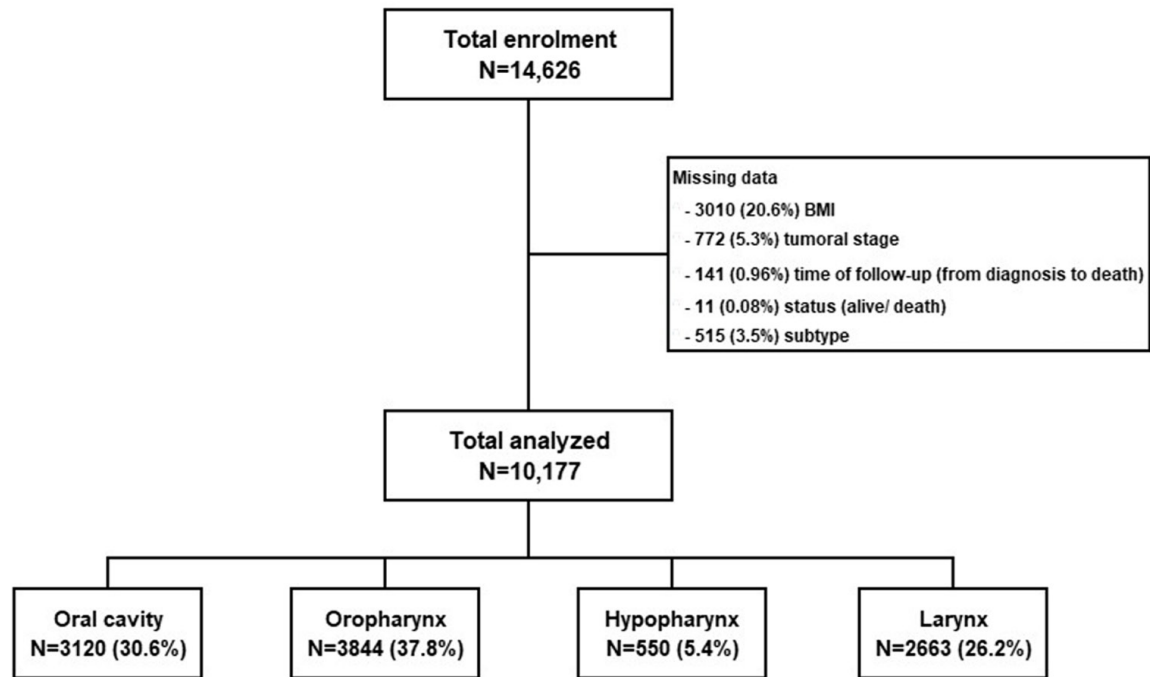
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## BMI and head and neck cancer survival

**Supplementary Table 1.** Studies of the INHANCE consortium included in the analysis

Study	Follow up	Reference	
Italy	Rome	2002-2012	Galli et al., 2009 [37]
	Milan	2001-2009	Bravi et al., 2013 [38]
	Aviano, Padua, Turin	2002-2005	Lagiou et al., 2009 [39]
Central Europe		1998-2010	Hashibe et al., 2006 [40]
UK		2011-2018	Ness et al., 2014 [41]
Boston		1998-2013	Peters et al., 2005 [42]
Los Angeles		1999-2014	Cui et al., 2006 [43]
Michigan		2008-2017	Arthur et al., 2013 [44]
North Carolina		2002-2013	Divaris et al., 2010 [45]
Toronto		2001-2017	Habbous et al., 2013 [46]
Buenos Aires		1998-2017	Szymańska et al., 2011 [47]
Sao Paulo		1991-2014	Boing et al., 2011 [48]



**Supplementary Figure 1.** Flowchart of the distribution of available data included in the analysis.

## BMI and head and neck cancer survival

**Supplementary Table 2.** Demographic, clinical, and behavioural characteristics of 10,177 HNC patients according to the INHANCE participating study

	Europe						North America						South America				Total					
	Italy N=342		Central Europe N=197		UK N=2999		Boston N=800		Los Angeles N=284		Michigan N=918		North Carolina N=1067		Toronto N=1880		Buenos Aires N=70		São Paulo N=1620		N=10,177	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Gender</b>																						
Female	67	19.6	48	24.4	737	24.6	209	26.1	51	18.0	252	27.5	238	22.3	409	21.8	11	15.7	232	14.4	2254	22.2
Male	275	80.4	149	75.6	2262	75.4	591	73.9	233	82.0	666	72.5	829	77.7	1471	78.2	59	84.3	1377	85.6	7912	77.8
Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	11	0.7	11	0.1
<b>Age at diagnosis (yrs), median (IQR)</b>																						
	62 (54-69)		57 (51-63)		61 (54-68)		59 (52-66)		53 (47-57)		60 (53-69)		59 (51-67)		62 (55-70)		60 (53-65)		57 (51-65)		60 (53-68)	
<b>HNC site</b>																						
Oral cavity	92	26.9	72	36.5	836	27.9	199	24.9	48	16.9	365	39.8	183	17.2	618	32.9	18	25.7	689	42.5	3120	30.6
Oropharynx	82	24.0	77	39.1	1294	43.1	423	52.9	141	49.6	350	38.1	359	33.6	794	42.2	17	24.3	307	19.0	3844	37.8
Hypopharynx	28	8.2	9	4.6	149	5.0	46	5.7	15	5.3	30	3.3	60	5.6	72	3.8	3	4.3	138	8.5	550	5.4
Larynx	140	40.9	39	19.8	720	24.0	132	16.5	80	28.2	173	18.8	465	43.6	396	21.1	32	45.7	486	30.0	2663	26.2
<b>BMI categories</b>																						
Underweight	12	3.5	17	8.6	108	3.6	45	5.6	9	3.2	41	4.5	39	3.7	76	4.0	6	8.5	148	9.1	501	4.9
Normal weight	153	44.7	93	47.2	1179	39.3	375	46.9	100	35.2	303	33.0	390	36.5	738	39.3	27	38.6	926	57.2	4284	42.1
Overweight	133	38.9	55	27.9	1081	36.1	271	33.9	116	40.8	317	34.5	370	34.7	667	35.5	27	38.6	421	26.0	3458	34.0
Obese	44	12.9	32	16.3	631	21.0	109	13.6	59	20.8	257	28.0	268	25.1	399	21.2	10	14.3	125	7.7	1934	19.0
<b>Education level</b>																						
No education	0	0.0	0	0.0	8	0.3	0	0.0	3	1.1	0	0.0	0	0.0	0	0.0	0	0.0	141	8.9	152	2.2
≤ Junior high school	170	69.4	42	22.5	128	4.6	21	2.7	22	7.7	0	0.0	77	7.2	0	0.0	55	79.7	768	48.5	1283	18.3
Some high school	28	11.4	61	32.6	1338	48.3	68	8.6	38	13.4	0	0.0	300	28.1	0	0.0	7	10.1	417	26.3	2257	32.3
High school graduate	11	4.5	38	20.3	335	12.1	240	30.5	64	22.5	0	0.0	301	28.2	0	0.0	2	2.9	194	12.2	1185	17.0
Technical school, some college	27	11.0	27	14.4	469	17.0	138	17.5	79	27.8	0	0.0	246	23.1	0	0.0	2	2.9	36	2.3	1024	14.6
≥ College graduate	9	3.7	19	10.2	491	17.7	321	40.7	78	27.5	0	0.0	143	13.4	0	0.0	3	4.4	28	1.8	1092	15.6
Missing	97	28.4	10	5.1	230	7.7	12	1.5	0	0.0	918	100	0	0.0	1880	100	1	1.4	36	2.2	3184	31.3
<b>Tumour Stage</b>																						
I-II	157	45.9	51	25.9	1180	39.4	222	27.8	232	81.7	251	27.3	431	40.4	566	30.1	44	62.9	309	19.1	3443	33.8
III-IV	185	54.1	146	74.1	1819	60.6	578	72.2	52	18.3	667	72.7	636	59.6	1314	69.9	26	37.1	1311	80.9	6734	66.2
<b>Smoking status</b>																						
Never	45	13.2	22	11.2	636	22.1	182	29.6	70	24.6	230	25.1	118	11.1	479	25.7	11	15.7	187	11.6	1980	20.1
Former	121	35.5	31	15.7	1664	57.7	100	16.3	92	32.4	303	33.1	279	26.1	997	53.4	19	27.1	370	22.9	3976	40.4
Current	175	51.3	144	73.1	584	20.2	332	54.1	122	43.0	382	41.8	670	62.8	390	20.9	40	57.2	1056	65.5	3895	39.5
Missing	1	0.3	0	0.0	115	3.8	186	23.3	0	0.0	3	0.3	0	0.0	14	0.7	0	0.0	7	0.4	326	3.2
<b>Pack-years for ever smokers, median (IQR)</b>																						
	35 (24-48)		33 (21-44)		26 (12-43)		27 (10-48)		33 (16-47)		-		47 (29-72)		30 (13-45)		38 (24-48)		42 (28-62)		34 (18-51)	
<b>Drinking status</b>																						
Never	25	7.6	32	16.3	762	25.4	44	6.2	36	12.8	98	10.7	102	9.6	297	23.0	10	14.3	187	11.6	1593	16.8
Ever	304	92.4	164	83.7	2237	74.6	662	93.8	246	87.2	815	89.3	964	90.4	995	77.0	60	85.7	1427	88.4	7874	83.2
Missing	13	3.8	1	0.5	0	0.0	94	11.8	2	0.7	5	0.5	1	0.1	588	31.3	0	0.0	6	0.4	710	7.0

## BMI and head and neck cancer survival

Treatment																						
No	63	18.5	2	1.0	13	0.4	71	13.7	0	0.0	0	0.0	5	0.5	28	1.5	0	0.0	28	1.8	210	2.3
Surgery only	40	11.7	33	16.8	643	21.5	0	0.0	0	0.0	220	26.3	176	18.2	325	17.7	0	0.0	526	33.5	1963	21.2
Surgery and radiation	21	6.2	102	51.8	403	13.4	0	0.0	0	0.0	103	12.3	218	22.5	202	11.0	0	0.0	609	38.8	1658	17.9
Radiation and/or chemotherapy	202	59.2	42	21.3	1614	53.8	447	86.3	0	0.0	430	51.5	437	45.1	1204	65.5	0	0.0	140	8.9	4516	48.7
Surgery and chemo ± radiation*	15	4.4	18	9.1	326	10.9	0	0.0	0	0.0	83	9.9	133	13.7	79	4.3	0	0.0	268	17.0	922	9.9
Missing	1	0.3	0	0.0	0	0.0	282	35.3	284	100	82	8.9	98	9.2	42	2.2	70	100	49	3.0	908	8.9
Status																						
Alive	184	53.8	69	35.0	2111	70.4	580	72.5	174	61.3	618	67.3	465	43.6	1357	72.2	45	64.3	920	56.8	6523	64.1
Dead	158	46.2	128	65.0	888	29.6	220	27.5	110	38.7	300	32.7	602	56.4	523	27.8	25	35.7	700	43.2	3654	35.9

Abbreviations: HNC = head and neck cancer, IQR = interquartile range, BMI = body mass index. \*Surgery and chemotherapy (with or without radiation).

**Supplementary Table 3.** Unadjusted analysis for the association between BMI and overall survival, by HNC site

Overall survival	Oral Cavity (N=3120)			Oropharynx (N=3844)			Hypopharynx (N=550)			Larynx (N=2663)			All HNC (N=10,177)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Underweight	1.63	1.56-1.71	<0.0001	2.63	2.14-3.23	<0.0001	2.15	1.93-2.39	<0.0001	1.71	1.59-1.84	<0.0001	2.00	1.80-2.22	<0.0001
Normal weight	1			1			1			1			1		
Overweight	0.80	0.69-0.93	0.004	0.63	0.48-0.83	0.001	1.16	0.99-1.34	0.06	0.62	0.52-0.74	<0.0001	0.68	0.66-0.69	<0.0001
Obese	0.73	0.53-0.99	0.041	0.58	0.44-0.75	<0.0001	0.87	0.45-1.69	0.69	0.67	0.59-0.77	<0.0001	0.63	0.53-0.75	<0.0001
P for linear trend	<0.0001			<0.0001			0.024			<0.0001			<0.0001		

Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval.

**Supplementary Table 4.** Unadjusted analysis for the association between BMI and HNC-specific survival, by HNC site

HNC-specific survival	Oral Cavity (N=3120)			Oropharynx (N=3844)			Hypopharynx (N=550)			Larynx (N=2663)			All HNC (N=10,177)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Underweight	1.85	1.65-2.07	<0.0001	2.76	1.90-4.00	<0.0001	2.56	1.46-4.49	0.001	1.44	1.12-1.85	0.005	2.11	1.85-2.42	<0.0001
Normal weight	1			1			1			1			1		
Overweight	0.74	0.64-0.87	<0.0001	0.40	0.18-0.87	0.021	0.92	0.84-1.01	0.09	0.54	0.43-0.68	<0.0001	0.55	0.47-0.65	<0.0001
Obese	0.64	0.54-0.75	<0.0001	0.37	0.15-0.96	0.042	0.81	0.28-2.37	0.71	0.62	0.28-1.36	0.23	0.51	0.33-0.77	0.002
P for linear trend	<0.0001			<0.0001			0.010			<0.0001			<0.0001		

Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval.

## BMI and head and neck cancer survival

**Supplementary Table 5.** Adjusted analysis\* for the association between BMI and overall and HNC-specific survival

	HR	ALL HNC	
		95% CI	P value
Overall survival	(N=2828)		
Underweight	1.49	1.01-2.21	0.045
Normal weight	1		
Overweight	0.87	0.81-0.93	<0.0001
Obese	0.90	0.84-0.97	0.006
HNC-specific survival	(N=2828)		
Underweight	1.23	0.75-2.01	0.40
Normal weight	1		
Overweight	0.77	0.70-0.84	<0.0001
Obese	0.84	0.64-1.10	0.21

\*For age at diagnosis, gender, tumour stage, education level, smoking status, years of smoking, cigarettes per day, drinking status, years of alcohol consumption, drinks per day, treatment and region. Reference: normal weight. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval.

## BMI and head and neck cancer survival

**Supplementary Table 6.** One-stage analysis\* for the association between BMI and overall and HNC-specific survival, by HNC site

	Oral Cavity			Oropharynx			Hypopharynx			Larynx			All HNC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Overall survival	(N=2573)			(N=3322)			(N=463)			(N=2309)			(N=8667)		
Underweight	1.54	1.18-2.01	0.015	1.94	1.51-2.48	<0.0001	2.06	1.39-3.07	0.0003	1.52	1.14-2.02	0.004	1.69	1.47-1.95	<0.0001
Normal weight	1			1			1			1			1		
Overweight	0.94	0.81-1.08	0.36	0.70	0.60-0.81	<0.0001	1.25	0.94-1.67	0.130	0.69	0.59-0.82	<0.0001	0.77	0.71-0.83	<0.0001
Obese	0.87	0.72-1.05	0.16	0.69	0.57-0.82	<0.0001	0.96	0.64-1.44	0.830	0.81	0.77-0.98	0.033	0.76	0.68-0.84	<0.0001
HNC-specific survival	(N=2573)			(N=3322)			(N=463)			(N=2309)			(N=8667)		
Underweight	1.25	0.78-2.01	0.36	1.44	0.91-2.26	0.120	1.83	0.94-3.55	0.075	0.98	0.55-1.73	0.93	1.32	1.02-1.71	0.035
Normal weight	1			1			1			1			1		
Overweight	1.10	0.86-1.41	0.44	0.55	0.40-0.75	0.0002	1.30	0.77-2.18	0.33	0.77	0.57-1.02	0.072	0.80	0.69-0.94	0.0051
Obese	1.10	0.80-1.53	0.56	0.55	0.37-0.81	0.001	1.32	0.66-2.66	0.43	1.03	0.73-1.47	0.86	0.86	0.71-1.05	0.13

\*Fixed effects for age at diagnosis, gender, tumour stage, education level, smoking status and drinking status; random effect: intercept for region. Reference: normal weight. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval.

**Supplementary Table 7A.** One-stage analysis\* for the association between BMI and overall survival, by HNC site and according to smoking habits

	Oral Cavity			Oropharynx			Hypopharynx			Larynx			All HNC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Never-smokers	(N=619)			(N=884)			(N=38)			(N=212)			(N=1753)		
Underweight	1.61	0.68-3.83	0.28	3.04	1.02-9.05	0.046	-	-	-	0.44	0.10-1.88	0.27	1.37	0.79-2.38	0.26
Normal weight	1			1			1			1			1		
Overweight	0.91	0.64-1.30	0.60	1.00	0.66-1.51	0.99	2.36	0.45-12.51	0.31	0.82	0.44-1.54	0.54	0.85	0.67-1.07	0.17
Obese	1.03	0.70-1.53	0.87	1.01	0.64-1.60	0.96	1.61	0.37-7.15	0.53	0.80	0.35-1.78	0.58	0.94	0.72-1.23	0.66
Ever-smokers**	(N=1389)			(N=1767)			(N=320)			(N=1592)			(N=5068)		
Underweight	1.40	1.01-1.94	0.043	1.72	1.26-2.35	0.0006	1.98	1.21-3.23	0.0064	1.60	1.14-2.27	0.0072	1.61	1.36-1.92	<0.0001
Normal weight	1			1			1			1			1		
Overweight	0.98	0.81-1.18	0.82	0.63	0.53-0.76	<0.0001	1.38	0.98-1.95	0.068	0.68	0.57-0.82	<0.0001	0.74	0.67-0.82	<0.0001
Obese	0.79	0.62-1.02	0.074	0.60	0.47-0.76	0.0003	1.03	0.64-1.68	0.89	0.79	0.64-0.99	0.037	0.70	0.61-0.79	<0.0001

\*Fixed effects for age at diagnosis, gender, tumour stage, education level, smoking status and drinking status; random effect: intercept for region. Reference: normal weight. \*\*Also adjusted for pack-years smoking. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval. - HR and CI not estimated for low sample size.

## BMI and head and neck cancer survival

**Supplementary Table 7B.** One-stage analysis\* for the association between BMI and HNC-specific survival, by HNC site and according to smoking habits

	Oral Cavity			Oropharynx			Hypopharynx			Larynx			All HNC		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Never-smokers	(N=619)			(N=884)			(N=38)			(N=212)			(N=1753)		
Underweight	0.38	0.05-3.02	0.36	1.62	0.13-2.06	0.71	-	-	-	-	-	-	0.39	0.12-1.31	0.13
Normal weight	1			1			1			1			1		
Overweight	1.10	0.58-2.10	0.76	0.75	0.32-1.77	0.51	0.94	0.11-8.12	0.95	0.59	0.20-1.75	0.34	0.83	0.54-1.27	0.38
Obese	1.91	0.98-3.74	0.059	0.42	0.13-1.32	0.14	0.21	0.01-5.29	0.34	1.80	0.41-7.93	0.44	1.12	0.68-1.83	0.66
Ever-smokers**	(N=1389)			(N=1767)			(N=320)			(N=1592)			(N=5068)		
Underweight	1.41	0.86-2.29	0.17	1.52	0.95-2.43	0.084	1.59	0.79-3.23	0.20	1.16	0.64-2.11	0.63	1.45	1.11-1.89	0.007
Normal weight	1			1			1			1			1		
Overweight	1.14	0.87-1.49	0.34	0.47	0.33-0.67	<0.0001	1.24	0.70-2.18	0.46	0.74	0.54-1.00	0.050	0.75	0.63-0.88	0.0006
Obese	0.87	0.59-1.30	0.50	0.58	0.38-0.89	0.012	1.36	0.65-2.83	0.42	0.91	0.63-1.31	0.62	0.77	0.62-0.96	0.019

\*Fixed effects on age at diagnosis, gender, tumour stage, education level, smoking status and drinking status; random effect: intercept for region. Reference: normal weight. \*\*Also adjusted for pack-years smoking. Abbreviations: BMI = body mass index, HNC = head and neck cancer, HR = hazard ratio, CI = confidence interval. - HR and CI not estimated for low sample size.