

## CANCER

# Body mass index and risk of head and neck cancer in a pooled analysis of case–control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium

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**Background** Head and neck cancer (HNC) risk is elevated among lean people and reduced among overweight or obese people in some studies; however, it is unknown whether these associations differ for certain subgroups or are influenced by residual confounding from the effects of alcohol and tobacco use or by other sources of biases.

**Methods** We pooled data from 17 case–control studies including 12 716 cases and the 17 438 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for associations between body mass index (BMI) at different ages and HNC risk, adjusted for age, sex, centre, race, education, tobacco smoking and alcohol consumption.

**Results** Adjusted ORs (95% CIs) were elevated for people with BMI at reference (date of diagnosis for cases and date of selection for

controls)  $\leq 18.5 \text{ kg/m}^2$  (2.13, 1.75–2.58) and reduced for BMI  $>25.0\text{--}30.0 \text{ kg/m}^2$  (0.52, 0.44–0.60) and BMI  $\geq 30 \text{ kg/m}^2$  (0.43, 0.33–0.57), compared with BMI  $>18.5\text{--}25.0 \text{ kg/m}^2$ . These associations did not differ by age, sex, tumour site or control source. Although the increased risk among people with BMI  $\leq 18.5 \text{ kg/m}^2$  was not modified by tobacco smoking or alcohol drinking, the inverse association for people with BMI  $>25 \text{ kg/m}^2$  was present only in smokers and drinkers.

**Conclusions** In our large pooled analysis, leanness was associated with increased HNC risk regardless of smoking and drinking status, although reverse causality cannot be excluded. The reduced risk among overweight or obese people may indicate body size is a modifier of the risk associated with smoking and drinking. Further clarification may be provided by analyses of prospective cohort and mechanistic studies.

**Keywords** BMI, head and neck cancer, smoking

## Introduction

Cancers of the oral cavity, pharynx and larynx—referred to collectively as head and neck cancer (HNC)—account for a half a million cancer diagnoses worldwide.<sup>1</sup> Although in Europe and North America ~75% of these cancers are attributed to tobacco smoke and alcohol consumption,<sup>2–4</sup> the large proportion of patients who are non-smokers and non-drinkers indicates that other factors may affect risk of these cancers. Most previous studies<sup>5–13</sup> have found that people with a body mass index (BMI)  $<18.5 \text{ kg/m}^2$  experience a higher risk of HNC, compared with people with a normal BMI (18.5 to  $<25.0 \text{ kg/m}^2$ ). Among overweight (25.0 to  $<30.0 \text{ kg/m}^2$ ) or obese ( $>30.0 \text{ kg/m}^2$ ) people, HNC risk appears to be lower than among those with a normal BMI.<sup>5–13</sup>

The independent effect of body size on HNC is difficult to assess because it is strongly affected by alcohol drinking and cigarette smoking,<sup>14–16</sup> the two major risk factors for these malignancies. Even following adjustment for alcohol and tobacco consumption, the influence of residual confounding cannot be easily discounted. The limited sample size of previous reports based on individual studies has hindered detailed examination of the association with body size in the small proportion of non-smokers and non-drinkers, among whom confounding by cigarette smoking and alcohol consumption would be especially minimized.

The International Head and Neck Cancer Epidemiology (INHANCE) Consortium has pooled epidemiologic studies of HNC to estimate the effects of risk factors on HNC risk.<sup>3</sup> The large number of cases assembled by INHANCE allowed us to estimate more precisely the association with BMI in non-smokers and non-drinkers, as well as in smokers and drinkers. We also examined other potentially important subgroups, such as tumour site, sex and age, as well as the

possible methodological issue of whether controls were selected from hospital populations or the general population. In addition to weight at the time of diagnosis, we also examined self-reported weight 2–5 years prior to diagnosis as an estimate of weight prior to weight loss secondary to disease, and also weight at age 20–30 years to evaluate the effects of early body size.

## Methods

Data pooling methods for the INHANCE consortium have been previously described in detail elsewhere.<sup>3</sup> The INHANCE consortium originally included 15 individual case–control studies (version 1.1), including 10 244 cases and 15 227 controls.<sup>17–30</sup> After our earlier publication,<sup>3</sup> four additional studies joined the INHANCE consortium including two multicentre studies based in the USA: the New York multicentre study<sup>31</sup> (covering New York City, Chicago, Hines, IL, Detroit, MI, New Hyde Park, NY, East Meadow, NY and Philadelphia) and the US multicentre study (covering metropolitan Atlanta, Los Angeles, Santa Clara and San Mateo counties south of San Francisco–Oakland, and the state of New Jersey),<sup>32</sup> and studies in Rome<sup>33</sup> and Boston.<sup>34</sup> In the current analysis, we excluded the Iowa study (556 cases and 760 controls)<sup>30</sup> that did not collect information about weight and height, and the Rome study (278 cases and 295 controls)<sup>33</sup> because only weight was collected. A total of 17 studies, including 9 in North America, 7 in Europe and 1 in South America (Table 1), contributed data to the current analyses that included 12 716 cases and 17 438 controls, which excluded 49 cases and 101 controls with missing data for age, sex or race/ethnicity and the site of origin of their tumour.

Cases were defined as newly diagnosed cancers of the oral cavity, pharynx, oral/pharynx not otherwise

**Table 1** Characteristics of the 12716 cases and the 17438 controls with data on body size<sup>a</sup>

Characteristic	Cases		Controls	
	<i>n</i>	%	<i>n</i>	%
Age (years)				
12–39	500	3.9	1135	6.5
40–45	706	5.6	1240	7.1
45–49	1364	10.7	1920	11.0
50–54	1934	15.2	2701	15.5
55–59	2346	18.4	1994	11.4
60–64	2199	17.3	2724	15.6
65–69	1786	14.0	2305	13.2
70–74	1205	9.5	1627	9.3
75–94	676	5.3	791	4.5
Sex				
Women	2759	21.7	5124	29.4
Men	9957	78.3	12314	70.6
Race				
Non-Hispanic White	8870	69.8	13691	78.5
Black	682	5.4	770	4.4
Hispanic	208	1.6	428	2.5
Asian	629	4.9	665	3.8
Other	136	1.1	178	1.0
Brazilian	2191	17.2	1706	9.8
Study location				
Italy multicentre	1261	9.9	2716	15.6
Latin America multicentre	2191	17.2	1706	9.8
IARC multicentre	1559	12.3	1676	9.6
Milan	416	3.8	1531	8.8
US multicentre	1114	8.8	1268	7.3
Los Angeles	417	3.3	1005	5.8
Central Europe	762	6.0	907	5.2
New York multicentre	1118	8.8	906	5.2
Tampa	207	1.6	897	5.1
Switzerland	516	4.1	883	5.1
Houston	829	6.5	865	5.0
Aviano	482	3.8	855	4.9
Boston	584	4.6	659	3.8
Seattle	407	3.2	607	3.5
Puerto Rico	350	2.8	521	3.0
France	323	2.5	234	1.3
North Carolina	180	1.4	202	1.2
Study design				
Hospital-based studies	9844	77.4	13 378	76.7
Population-based studies	2872	22.6	4060	23.3

(continued)

**Table 1** Continued

Characteristic	Cases		Controls	
	<i>n</i>	%	<i>n</i>	%
Cigarette smoking status				
Never	1341	10.5	6465	37.1
Ever	11 372	89.5	10 959	62.9
Missing	3		14	
Pack-years of cigarette smoking				
Never	1901	15.1	6827	39.6
1–10	858	6.8	2539	14.7
11–20	1146	9.1	1986	11.5
21–30	1620	12.9	1747	10.1
31–40	1838	14.6	1391	8.1
41–50	1546	12.3	977	5.7
>50–441	3681	29.2	1790	10.4
Missing	126		181	
Alcohol drinking status				
Never	1786	14.1	4462	25.6
Ever	10915	85.9	12964	74.4
Missing	15		12	
Number of alcohol drinks per day				
Never	1786	14.7	4462	26.4
0 to <1	2192	18.1	4761	28.2
1 to <3	2338	19.3	3618	21.4
3 to <5	1522	12.5	1725	10.2
5 to 8512	4290	35.4	2305	13.7
Missing	588		567	
Height (in metres)				
0.65–1.64	3168	27.2	4434	26.9
1.65–1.69	2145	18.4	3138	19.0
1.70–1.74	2584	22.2	3508	21.3
1.75–2.13	3764	32.3	5414	32.8
Subsite of tumour				
Oral cavity	3740	29.4		
Oral cavity/pharynx NOS	3690	29.0		
Oropharynx	917	7.2		
Hypopharynx	1226	9.6		
Larynx	2837	22.3		
Head and neck overlap	306	2.4		
Histology of tumour				
Squamous cell	800	71.4		
Other	320	28.6		
Unknown	3596			

<sup>a</sup>INHANCE pooled case–control study of HNC. IARC = International Agency on Research for Cancer.

specified (NOS) or larynx. For each study, controls were frequency-matched on age and sex, and for some studies: centre (Italy multicentre, Central Europe, IARC multicentre and Latin America studies), hospital (France study), ethnicity (Tampa and Los Angeles studies) and neighbourhood (Los Angeles study). The date of reference was defined as the date of diagnosis for cases and the date of selection for controls with the exception of the Seattle study. In the Seattle study, the date of reference for controls was selected at random from among the possible case diagnosis dates.<sup>29</sup> The wording of interview questions was compared across studies to determine data similarities. Variables for ethnicity, education, tumour site and histology, cigarette smoking, other tobacco habits, alcohol consumption, height and weight were pooled across studies, as described in detail elsewhere<sup>3</sup> and in brief below.

All height and weight variables were self-reported at the time of interview. Adult height was missing for 1055 cases and 944 controls. Because each study queried weight for different time periods, the total number of cases and controls differ by analysis. Weight at the date of reference was self-reported for 11 547 cases and 15 924 controls with the exception of Central Europe and Seattle. Weight 2–5 years prior to reference was collected for 7654 cases and 9799 controls (from studies: Central Europe, New York Multicentre, Seattle, Boston, Latin America and IARC multicentre studies), and weight between 20 and 30 years of age for 7654 cases and 9799 controls (from studies: Central Europe, Puerto Rico, Los Angeles, Latin America, IARC multicentre, Italy multicentre and US multicentre studies). BMI values were calculated as weight (in kilograms) divided by height squared (in square metres). We were not able to systematically verify self-reported height and weight; therefore, we included all BMI values. Few subjects had values outside the physiological range (BMI < 11 or >60.0 kg/m<sup>2</sup>); specifically, three cases and five controls for BMI at reference, four cases and four controls for BMI 2–5 years prior to reference and six cases and two controls for BMI at age 20–30 years had BMI values >60.0 kg/m<sup>2</sup>. BMI values were categorized according to the World Health Organization definitions ( $\leq 18.5$ , >18.5–25.0, >25.0–30.0, >30.0 kg/m<sup>2</sup>).<sup>35</sup> Height was categorized using quartiles of the control distribution.

We used the definitions of smoking of cigarettes, pipes and cigars, and alcohol drinking categories adopted in a previous INHANCE publication.<sup>3</sup> Although questions about tobacco use varied across studies, never users of cigarettes, pipes and cigars did not exceed either 1 year of cigarette smoking, 100 cigarettes in a lifetime or ever smoked 'regularly' (France and Central Europe studies). Pack-years of cigarette smoking was calculated by multiplying packs (defined as 20 cigarettes) of cigarettes per day and number of years smoking. In the alcohol section of the study

questionnaires, subjects were asked if they had been alcohol drinkers, then asked subsequent questions on frequency of drinking, duration of drinking and different types of alcoholic beverages consumed (beer, wine, hard liquors and aperitif). Definition of never drinkers also varied by study, from 0 drinks in a lifetime (France, Central Europe, Aviano, Milan, Italy multicentre and Switzerland studies) to <4 drinks per month (North Carolina study).<sup>3</sup> To handle the different volume specification for each type of alcoholic beverage by study, the number of drinks per day was calculated by the frequency of consumption of each alcoholic beverage type weighted by the corresponding duration with the exception of France, Iowa and Tampa studies, in which the average of the frequency of all alcoholic beverage type was used in lieu of missing data for duration.<sup>3</sup>

For missing data on education level (703 cases and 487 controls for the analysis on BMI at diagnosis; 367 cases and 227 controls for the analysis on BMI 2–5 years prior to diagnosis; 318 cases and 229 controls for the analysis on BMI at age 20–30 years), we applied multiple imputation with the PROC MI procedure in SAS Institute Inc software 9.0 (Cary, NC), for the studies within each of the four geographic regions. We used a logistic regression model<sup>36</sup> to predict education level with age, sex, race/ethnicity, study and case–control status.

Unconditional logistic models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Minimally adjusted models controlled for age, study, ethnicity and education level (categorical, see Table 1). Multivariate-adjusted models were further adjusted for pack-years of cigarette smoking (continuous) and drinks per day (continuous). Because cigarette smoking status was associated with BMI in our populations (Supplementary Table 1 available as Supplementary data at *IJE* online), we were concerned about residual confounding by cigarette smoking. Therefore, we explored separate models with alternate definitions of cigarette smoking, including log-transformed cigarette-years, square root of pack-years with ever smoking status and duration of cigarette smoking with ever smoking status.<sup>37,38</sup> The *P*-values for linear trend were calculated using the ordinal values for the categorical variable in logistic regression models.

Multivariate-adjusted models among all subjects were further stratified by cigarette smoking and alcohol drinking status (non-drinking and non-smoking, and non-smoking and non-drinking subjects), age (<50,  $\geq 50$  years), sex, study centre and geographical region (Europe, North America, Latin America and Asia) and whether the study collected population-based or hospital-based controls. Cigarette smokers were further stratified by smoking status (never, current, former), duration of smoking ( $\leq 20$ , >20 <40,  $\geq 40$  years), number of cigarettes smoked per day (<15, 15–20, 21–30,  $\geq 31$ ) among current smokers, and for former smokers time since quitting

smoking ( $\leq 10$ ,  $>10$  to  $<20$ ,  $\geq 20$  years). HNC cases were stratified by tumour histology and site. Effect measure modification was evaluated by testing for deviation from a multiplicative interaction model, using the log-likelihood ratio test to compare the fit of logistic models with and without an interaction term. Between-study heterogeneity was also examined using the likelihood ratio test.

## Results

### Study population characteristics

A total of 12 716 cases and 17 438 controls had anthropometry data. Among these participants, cases

were older and more likely to be male, shorter in stature ( $<1.65$  m), cigarette smoker and alcohol drinker compared with controls (Table 1). Furthermore, cases were heavier cigarette smokers and alcohol drinkers than controls. Most (71.4%) cases were squamous cell carcinomas. Approximately 70% of cases were diagnosed with cancers of the oro- and hypo-pharynx or larynx, and 30% of the cases were diagnosed with cancers of the oral cavity. A majority of the studies selected controls from hospital patients.

### BMI

Lean subjects at reference ( $\text{BMI} \leq 18.5 \text{ kg/m}^2$ ) had twice the risk of HNC (multivariate-adjusted OR = 2.13, 95% CI 1.75–2.58; Table 2), compared

**Table 2** Adjusted<sup>a</sup> ORs and 95% CIs for the association between HNC and BMI

BMI measures	Cases n (%)	Controls n (%)	Minimally-adjusted <sup>b</sup>		Multivariate-adjusted <sup>c</sup>	
			OR	(95% CI)	OR	(95% CI)
BMI ( $\text{kg/m}^2$ ) at reference <sup>d,e</sup>						
<18.5	918 (8.7)	382 (2.5)	2.57	(2.20–2.99)	2.13	(1.75–2.58)
18.5–24.9	5749 (54.6)	6255 (41.5)	1.00		1.00	
25.0–29.9	2855 (27.1)	6069 (40.3)	0.47	(0.41–0.53)	0.52	(0.44–0.60)
$\geq 30.0$	1011 (9.6)	2359 (15.7)	0.43	(0.35–0.53)	0.43	(0.33–0.57)
P-value for study heterogeneity			<0.01		<0.01	
P for trend <sup>f</sup>			<10 <sup>-6</sup>		<10 <sup>-6</sup>	
BMI ( $\text{kg/m}^2$ ) at 2–5 years before reference <sup>g</sup>						
<18.5	481 (8.4)	203 (3.6)	1.88	(1.06–3.33)	1.56	(0.80–3.02)
18.5–24.9	3159 (55.4)	2456 (43.0)	1.00		1.00	
25.0–29.9	1523 (26.7)	2072 (36.3)	0.55	(0.44–0.68)	0.57	(0.48–0.68)
$\geq 30.0$	538 (9.4)	980 (17.2)	0.43	(0.31–0.61)	0.46	(0.30–0.72)
P-value for study heterogeneity			<0.01		<0.01	
P-value for trend <sup>f</sup>			0.000295		0.0011	
BMI ( $\text{kg/m}^2$ ) between 20 and 30 years of age <sup>h</sup>						
<18.5	415 (6.3)	579 (6.7)	0.99	(0.80–1.22)	0.91	(0.72–1.15)
18.5–24.9	4708 (71.9)	5911 (68.6)	1.00		1.00	
25.0–29.9	1232 (18.8)	1748 (20.3)	0.88	(0.74–1.05)	0.88	(0.73–1.04)
$\geq 30.0$	191 (2.9)	375 (4.4)	0.66	(0.48–0.91)	0.62	(0.44–0.86)
P-value for study heterogeneity			<0.01		0.03	
P-value for trend <sup>f</sup>			0.13		0.11	

<sup>a</sup>INHANCE pooled case-control study of HNC.

<sup>b</sup>Adjusted for age, sex, study centres, race and education level.

<sup>c</sup>Adjusted for age, sex, race, education level, study centres, pack-year of cigarette smoking, lifetime duration of pipe use, lifetime duration of cigar use and alcohol drinks per day.

<sup>d</sup>Date of reference is defined as the date of diagnosis for cases and date of selection for controls.

<sup>e</sup>Aggregate estimates are based on data from the following studies: France, Milan, Tampa, Puerto Rico, Switzerland, North Carolina, Aviano, Italy multicentre, Houston, Boston, New York, Los Angeles and South America.

<sup>f</sup>P-values for linear trend was calculated using the ordinal values for the categorical variable.

<sup>g</sup>Aggregate estimates are based on data from the following studies: Central Europe, New York, Seattle, Boston, South America and IARC Multicentre.

<sup>h</sup>Aggregate estimates are based on data from the following studies: Italy Multicentre, Centrale Europe, Los Angeles, Puerto Rico, South America and IARC Multicentre.

with subjects with a BMI between  $>18.5$  and  $25.0\text{ kg/m}^2$ . Conversely, HNC risk was inversely associated with being overweight (BMI  $>25.0$ – $30.0\text{ kg/m}^2$ ) or obese (BMI  $>30.0\text{ kg/m}^2$ ) at reference (multivariate-adjusted OR = 0.52, 95% CI 0.44–0.60; multivariate-adjusted OR = 0.43, 95% CI 0.33–0.57, respectively; Table 2), adjusting for pack-years of cigarette smoking, duration of cigar and pipe smoking and duration of alcohol consumption (Figure 1).

Comparing the minimally adjusted and the multivariate-adjusted ORs, it is evident that pack-years of cigarette smoking, lifetime duration of pipe use, lifetime duration of cigar use and alcohol drinks per day did not meaningfully confound the association between BMI and HNC risk. However, we further evaluated the influence of possible residual confounding from cigarette smoking among all subjects by

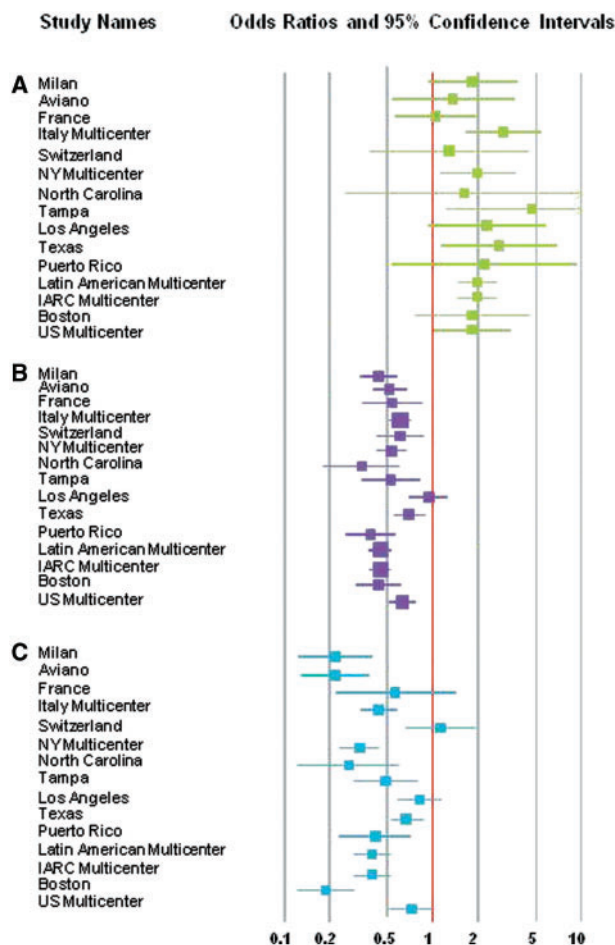
controlling for alternative definitions of cigarette smoking (including log-transformed cigarette-years, square root of pack-years with ever smoking status and duration of cigarette smoking with ever smoking status);<sup>37,38</sup> however, these alternate definitions of cigarette smoking did not alter the results for BMI (data not shown).

Results for BMI 2–5 years prior to the reference date were similar to the results for BMI at reference (Table 2). Furthermore, BMI  $>30.0\text{ kg/m}^2$  at age 20–30 years was associated with a lower risk of HNC (multivariate-adjusted OR = 0.62, 95% CI 0.44–0.86) compared with subjects with BMI  $>18.5$ – $25.0\text{ kg/m}^2$ . No association was found between leanness (BMI  $<18.5\text{ kg/m}^2$ ) at age 20–30 years and risk of HNC (multivariate-adjusted OR = 0.91, 95% CI 0.72–1.15). Additional analyses restricted to studies that reported all three BMI time points (including BMI at reference, 2–5 years prior to reference and at age 20–30 years) were not undertaken due to the small numbers from two studies (Latin American and IARC multicentre studies).

The direction of the risk estimates found in Table 2 was similar to those for individual studies, although the magnitude of the association differed significantly across studies ( $P$ -value for between-study heterogeneity was  $<0.01$ ), and there were no patterns by geographical region (Supplementary Table 2 available as Supplementary data at *IJE* online). The ORs and 95% CIs from random effects models (data not shown) were similar to those shown in Table 2 from fixed effect models.

### Effect measure modification by cigarette smoking and alcohol consumption

Among never tobacco smokers and never alcohol drinkers (Table 3), the associations for overweight (multivariate-adjusted OR = 0.94, 95% CI 0.49–1.80) and obese (multivariate-adjusted OR = 0.95, 95% CI 0.47–1.91) subjects were attenuated towards the null, whereas lean subjects at reference experienced an elevated risk of HNC (multivariate-adjusted OR = 3.13, 95% CI 0.73–13.40). The elevated risk associated with leanness was sustained for BMI 2–5 years prior to reference and for BMI at age 20–30 years among never tobacco smokers and never alcohol drinkers. Overweight and obesity were not associated with a lower risk of HNC at BMI 2–5 years before reference or at age 20–30 years (Table 3). Supplementary Tables S3 and S4 (available as Supplementary data at *IJE* online) show BMI associations stratified by tobacco use only and adjusted for alcohol intake, and stratified by alcohol use only adjusted for tobacco use, respectively. Overall, leanness at reference was inversely associated with HNC risk in all strata. BMI  $>25\text{ kg/m}^2$  was associated with HNC risk in all strata with the exception of never tobacco users ( $>25.0$ – $30.0\text{ kg/m}^2$ : multivariate-adjusted OR = 0.84, 95% CI 0.70–1.00;  $>30\text{ kg/m}^2$ : multivariate-adjusted



**Figure 1** Forest plot of study-specific ORs and 95% CIs for the association between HNC risk and BMI reported at reference with categories of  $<18.5\text{ kg/m}^2$  (leanness, A),  $25.0$  to  $<30.0\text{ kg/m}^2$  (overweight, B) and  $30.0$ – $60.0\text{ kg/m}^2$  (obese, C), compared with  $18.5$  to  $<25.0\text{ kg/m}^2$  (normal). Studies are weighted according to the inverse of the variation of the log OR. The size of the boxes indicates the variance of the log OR.

**Table 3** Multivariate-adjusted ORs and 95% CIs for the association between HNC and BMI by alcohol drinking and cigarette smoking status<sup>a</sup>

BMI measures	Among never tobacco smokers and never alcohol drinkers				Among ever tobacco smokers and ever alcohol drinkers			
	Case n (%)	Control n (%)	OR <sup>b</sup>	(95% CI)	Case n (%)	Control n (%)	OR <sup>c</sup>	(95% CI)
BMI (kg/m <sup>2</sup> ) at reference <sup>d,e</sup>								
<18.5	40 (8.3)	118 (4.8)	3.13	(0.73–13.40)	650 (7.7)	167 (2.1)	2.01	(1.60–2.52)
18.5–24.9	183 (38.0)	1017 (41.4)	1.00		4794 (55.0)	3287 (42.0)	1.00	
25.0–29.9	145 (30.0)	859 (35.0)	0.94	(0.49–1.80)	2271 (26.1)	3222 (41.2)	0.50	(0.45–0.56)
≥30.0	113 (23.5)	461 (18.8)	0.95	(0.47–1.91)	695 (8.0)	1142 (14.6)	0.38	(0.30–0.49)
P-value for study heterogeneity				0.02				
P for trend <sup>f</sup>				0.49	<10 <sup>-6</sup>			
BMI (kg/m <sup>2</sup> ) 2–5 years before reference <sup>g</sup>								
<18.5	28 (12.0)	81 (8.8)	2.64	(1.50–4.67)	245 (5.4)	73 (2.3)	1.39	(0.80–2.44)
18.5–24.9	93 (39.9)	419 (45.5)	1.00		2598 (57.7)	1335 (42.5)	1.00	
25.0–29.9	70 (30.0)	271 (29.5)	0.97	(0.67–1.41)	1259 (28.0)	1196 (38.1)	0.58	(0.49–0.68)
≥30.0	42 (18.0)	149 (16.2)	1.09	(0.70–1.71)	398 (8.8)	539 (17.1)	0.42	(0.29–0.60)
P-value for study heterogeneity				0.02	0.03			
P-value for trend <sup>f</sup>				0.17	0.00042			
BMI (kg/m <sup>2</sup> ) between 20 and 30 years of age <sup>h</sup>								
<18.5	24 (10.8)	99 (8.9)	1.76	(0.98–3.19)	326 (5.9)	271 (5.7)	0.88	(0.73–1.07)
18.5–24.9	135 (60.5)	743 (66.6)	1.00		4038 (73.2)	3333 (69.6)	1.00	
25.0–29.9	50 (22.4)	218 (19.5)	1.26	(0.84–1.90)	1018 (18.4)	1001 (20.9)	0.82	(0.73–0.91)
≥30.0	14 (6.3)	56 (5.0)	1.15	(0.57–2.35)	137 (2.5)	185 (3.9)	0.50	(0.39–0.65)
P-value for study heterogeneity				0.08	0.36			
P for trend <sup>f</sup>				0.90	<10 <sup>-5</sup>			

<sup>a</sup>INHANCE pooled case-control study of HNC.

<sup>b</sup>Adjusted for age, sex, study centres, race and education level.

<sup>c</sup>Adjusted for age, sex, race, education level, study centres, pack-year of cigarette smoking, lifetime duration of pipe use, lifetime duration of cigar use and alcohol drinks per day.

<sup>d</sup>Date of reference is defined as the date of diagnosis for cases and date of selection for controls.

<sup>e</sup>Aggregate estimates are based on data from the following studies: France, Milan, Tampa, Puerto Rico, Switzerland, Aviano, Italy multicentre, Houston, Boston, New York, Los Angeles and South America.

<sup>f</sup>P-values for linear trend was calculated using the ordinal values for the categorical variable.

<sup>g</sup>Aggregate estimates are based on data from the following studies: Central Europe, New York, Seattle, Boston, South America and IARC Multicentre.

<sup>h</sup>Aggregate estimates are based on data from the following studies: Italy Multicentre, Central Europe, Los Angeles, Puerto Rico, South America and IARC Multicentre.

OR = 0.82, 95% CI 0.65–1.02; Supplementary Table 5 available as Supplementary data at *IJE* online).

Among tobacco users, we further examined the relationship between BMI and risk of HNC by characteristics of smoking habits (Supplementary Tables 5–7 available as Supplementary data at *IJE* online). Similar to results presented overall (Table 2), obesity (at reference, 2–5 years prior to reference and at age 20–30 years) was associated with lower risk of HNC among both current and former tobacco users (Supplementary Table 5 available as Supplementary data at *IJE* online). Leanness was associated with higher risk of HNC among current smokers (multivariate-adjusted OR = 2.11, 95% CI 1.48–3.01; Supplementary Table 5 available as Supplementary

data at *IJE* online), persisted for current smoking of <15, 15–20 and 21–30 cigarettes/day, but was weaker, albeit imprecise, for smokers of >30 cigarettes/day (multivariate-adjusted OR = 1.27, 95% CI 0.79–2.03; Supplementary Table 6 available as Supplementary data at *IJE* online). Current smokers had a 51 and 62% lower risk, respectively, associated with being overweight or obese, compared with current smokers with BMI >18.5–25.0 kg/m<sup>2</sup> (multivariate-adjusted OR = 0.49, 95% CI 0.43–0.56 and OR = 0.38, 95% CI 0.27–0.54, respectively, Supplementary Table 5 available as Supplementary data at *IJE* online), regardless of number of cigarettes per day (Supplementary Table 6 available as Supplementary data at *IJE* online). The multivariate-adjusted ORs for BMI at

reference and 2–5 years from reference were slightly closer to the null for former tobacco users than those observed for current tobacco users ( $P$ -value for interaction was  $\leq 0.0001$ ; Supplementary Table 5 available as Supplementary data at *IJE* online). As the number of years since quitting increased, the decreased risk associated with leanness diminished (Supplementary Table 7 available as Supplementary data at *IJE* online). Results were similar whether any tobacco product (data not shown) or cigarette tobacco (as shown in tables presented here) were considered.

The inverse association for obesity appeared to be slightly stronger for heavier drinkers than for lighter drinkers or non-drinkers (Supplementary Table 8 available as Supplementary data at *IJE* online).

### Effect measure modification by other factors

Although the estimates for leanness, compared with BMI 18.5–25.0 kg/m<sup>2</sup>, were consistently elevated for risk of site-specific HNC, the ORs were stronger, ranging from 2.20 to 2.85, for squamous cell carcinomas risk of the oral cavity, hypopharynx and oropharynx compared with the  $\sim 1.6$  fold higher risk of laryngeal/oral cancer (Supplementary Table 9 available as Supplementary data at *IJE* online). The inverse associations with larger body size also varied by site-specific HNC risk but all estimates exhibited a decreased association (Supplementary Table 9 available as Supplementary data at *IJE* online). The association between body size and HNC risk was in similar directions for both men and women (Supplementary Table 10 available as Supplementary data at *IJE* online), although the magnitude of the association for BMI at reference was significantly different than that for men ( $P$ -value for interaction was 0.004). Age was also an effect measure modifier for leanness at reference and 2–5 years prior to reference, although estimates for overweight and obesity were similar for subjects <50 and  $\geq 50$  years (Supplementary Table 11 available as Supplementary data at *IJE* online). Supplementary Table 12 (available as Supplementary data at *IJE* online) displays the ORs for BMI by the type of control selection used in the study designs. ORs were similar despite the source of controls for BMI at reference and BMI at age 20–30 years, although the association for BMI 2–5 years prior to reference was stronger for studies with hospital-based controls compared with those with population-based controls.

## Discussion

In a pooled analysis of 17 international studies, we found that lean subjects were at higher risk of HNC, whereas heavy subjects were at a lower risk, compared with subjects with a normal body size, after adjustment for major HNC risk factors, cigarette smoking and alcohol drinking. These results confirm

the inverse association between BMI and HNC risk observed in previous studies.<sup>5–13</sup> Although these individual studies had fewer subjects who were non-smokers and non-drinkers to obtain estimates that were independent of smoking and alcohol use. We found that the elevated risk of HNC observed among lean subjects was evident among cigarette smokers and alcohol drinkers, as well as non-smokers and non-drinkers. However, the reduced risk related to higher BMI was limited only to cigarette smokers and alcohol drinkers in our analysis. Furthermore, examination of stratification by only tobacco use or only alcohol use suggested that the association between BMI and HNC risk was more confounded by tobacco use.

One explanation for our findings is that, in the time shortly before diagnosis, undiagnosed cancer lesions in the head and neck may cause dysphagia or odynophagia or may alter taste and appetite, leading to a reduction of overall caloric intake and weight loss. For example, in a study of 407 patients with newly diagnosed second primary or recurrent tumours, on average, a 5–10% weight loss before diagnosis in  $\sim 30$ –53% of cases was observed.<sup>39</sup> Reported weight, therefore, may misrepresent usual adult weight, which may be the more biologically relevant time frame. A 5–10% weight loss prior to diagnosis of cases may shift some cases into a lower BMI category at the time of study interview. If it is assumed that 25–50% of the reportedly lean subjects in our study had a ‘true’ normal adult body size then the corrected unadjusted OR for leanness would be 2.01 (95% CI 1.76–2.29) to 1.21 (95% CI 1.05–1.40). These estimates suggest that misclassification bias would need to be quite prevalent before risk estimates for leanness are significantly attenuated towards the null and thus modify our conclusions. Lastly, assuming 25% of our reportedly lean cases had a normal adult BMI and 25% of our reportedly normal weight cases had a true overweight BMI during adulthood, the OR for leanness would move farther from the null (OR = 2.65, 95% CI 2.32–3.02), whereas the OR for overweight would move towards the null (OR = 0.97, 95% CI 0.92–1.03), indicating the robustness of leanness estimates to the influence of differential misclassification, but casting some doubt on our estimates for overweight subjects. Furthermore, we found that leanness self reported 2–5 years prior to reference was also associated with elevated risk of HNC. In aggregate, these observations suggest that recent weight loss in cases is unlikely to cause a substantial bias to our observed results for leanness at reference (at diagnosis for cases).

Obesity, but not leanness, between 20 and 30 years of age was associated with lower risk for HNC. However, among people who never smoked or drank, data suggested an increase in risk with leanness and little to no association with being overweight or obese. Taken together with results for



BMI over the life course, a predisposition for leanness at a young age may increase risk of HNC in subjects who do not drink or smoke. In contrast, drinkers and smokers who were also overweight or obese at any age appear to have a lower risk of HNC.

Elevated risks among lean subjects and reduced risks among overweight and obese subjects have also been found for other smoking-related malignancies, including cancers of the lung<sup>40–45</sup> and squamous cell carcinoma of the esophagus.<sup>46</sup> These consistent findings from prospective cohort and retrospective case-control studies suggest that weight loss due to pre-existing conditions is unlikely to account for the observed associations. Moreover, exclusions of people who died in the first 5 years of follow-up and those with pre-existing disease in one prospective study did not significantly alter results,<sup>42</sup> which further suggests weight loss measured close to disease onset, such as in case-control studies represented here, does not appreciably contribute to exposure misclassification. These results, however, do not provide additional insight to whether cigarette smoking confounds or modifies the relationship between body size and risk of these smoking-related cancers. In the prospective studies of lung cancer,<sup>41,42,44</sup> the associations between leanness and mortality or incidence was minimally affected when adjusted for smoking, and weaker, although still evident, in non-smokers.<sup>41,42,44</sup>

Another possible explanation for our BMI findings stratified by alcohol/smoking status is that the underlying etiology and molecular mechanisms of smoking-related malignancies do not apply to those that develop in non-smokers.<sup>47</sup> For example, in lung cancer,<sup>47</sup> it has been shown that the somatic alterations in key tumour suppressor and oncogenes, risk factors and clinical features differ among smokers and non-smokers. If this is also true for tumours of the head and neck, it is possible that differences we observed in effect estimates between smokers and non-smokers may indicate true modification of risk.

Inconsistent definitions of a cigarette smoker and an alcohol drinker across studies may have led to the inclusion of some individuals who minimally used tobacco or alcohol into the 'never user of tobacco' and 'never drinker' categories as defined in this study<sup>3,44</sup> and in a study of lung cancer,<sup>44</sup> which may be a potential source of study heterogeneity detected in our effect estimates. However, estimated ORs for individual studies were in similar directions and differed only in the magnitude of the association. The exact sources of differences between studies are unknown, but our stratified analyses suggest that they are unlikely to be due to geographical region or sources of controls. The accuracy of self-reported height and weight is high for men and women but slightly lower for obese individuals.<sup>48</sup> Yet, even small underestimations of weight, accompanied by

overestimations of height, can shift an individual's BMI into a lower category. A downward shift in BMI, calculated from self-reported height and weight in our study, is likely to be non-differential with respect to case-control status. Our results for BMI at age 20–30 years self-reported at reference may be particularly prone to random misclassification and may explain why these estimates are closer to the null. We were further limited to evaluating the association with body size since we only had information on BMI, which is a measure of overall adiposity.<sup>49</sup>

There has been limited research on connections between leanness and likely mechanisms of head and neck carcinogenesis, although altered caloric absorption and utilization as well as levels of oxidative stress markers and DNA adducts have been proposed to mediate the relationship between body size and HNC risk.<sup>14–16,50–55</sup> Some,<sup>50,51</sup> but not all, studies have shown that lean, compared with heavy but otherwise healthy, adults have higher urinary levels of 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage that is also elevated in smokers.<sup>52–54</sup> This relationship was stronger<sup>51</sup> or only evident<sup>53</sup> among cigarette smokers but not non-smokers. Similarly, DNA adducts, which represent an integrated indicator of exposure, metabolism and DNA repair, have also been observed to be higher in lean, compared with overweight, smokers.<sup>55</sup> If greater propensity for elevated levels of oxidative stress markers and DNA adducts explains the association between leanness and higher HNC risk among smokers, we would not expect to have observed a higher risk of HNC for lean people regardless of smoking status, and an inverse association with overweight and obese people only among smokers and drinkers. Moderate smokers, who on average weigh less than non-smokers,<sup>14–16</sup> despite similar caloric intakes, have been hypothesized to have higher smoking-induced metabolism and caloric utilization or loss due to faster bowel motility.<sup>14</sup> However, the distribution of BMI in our control populations was unrelated to number of cigarettes smoked per day, and the lower risk for higher BMI and elevated risk for leanness persisted across categories of number of cigarettes smoked per day. Additional studies are needed to explore biological pathways that mediate the relationship between body size and head and neck and other smoking-related cancers.

Based on a large pool of case-control studies, our findings provide the strongest evidence to date that leanness is a risk factor for HNC independent of the confounding effects of cigarette smoking and alcohol drinking. Stronger tests of the relationship between BMI and HNC could come from large prospective cohorts to eliminate the possibility of bias due to pre-existing conditions, as well as functional studies, to explain the relationship between body size and HNC risk. Although only a small portion of adults

are lean,<sup>56</sup> our findings, if confirmed, may shed light on biological mechanisms independent of tobacco smoke and ethanol consumption.

## Supplementary Data

Supplementary data are available at *IJE* online.

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### KEY MESSAGES

- Leanness near the time of diagnosis was associated with higher risk of HNC among all participants, including those who did not drink alcohol or smoke cigarettes.
- Excess adiposity may be associated with lower risk of HNC, although the relationship may be limited to drinkers and smokers.

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