Title: Measured adiposity in relation to head and neck cancer risk in the European Prospective Investigation into Cancer and Nutrition

Heather A Ward[1 §], Petra A Wark[1], David C Muller[1], Annika Steffen[2], Mattias Johansson [3,27], Teresa Norat[1], Marc J Gunter[1,3], Kim Overvad[4, 5], Christina C Dahm[4], Jytte Halkjær[6], Anne Tjønneland[6], Marie-Christine Boutron-Ruault[7,8], Guy Fagherazzi[7,8] , Sylvie Mesrine[7,8], Paul Brennan[3], Heinz Freisling[3], Kuanrong Li[3], Rudolf Kaaks[9], Antonia Trichopoulou[10, 11], Pagona Lagiou[11, 12, 13], Salavatore Panico[14], Sara Grioni[15], Rosario Tumino[16], Paolo Vineis[1,17], Domenico Palli[18], Petra HM Peeters[1,19], H.Bas. Bueno-de-Mesquita[1,20], Elisabete Weiderpass[21-24], Antonio Agudo[26], Jose Ramón Quirós[27], Nerea Larrañaga [28,32], Eva Ardanaz [29,32], José María Huerta[30,32], María-José Sánchez[31,32], Göran Laurell[33], Ingegerd Johansson[34], Ulla Westin[35], Peter Wallström[36], Kathryn E Bradbury[37], Nicholas J Wareham[38], Kay-Tee Khaw[39], Clare Pearson[1,40], Heiner Boeing[2*], Elio Riboli[1]*

[§] Corresponding author. Email address: heather.ward@imperial.ac.uk; telephone 011 44 (0)20 7594 5081 ; Fax 020 7594 3456.

*These authors contributed equally to this work

Author affiliations:

[1] School of Public Health, Imperial College, St Mary's Campus, London W2 1PG, UK

[2] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

[3] International Agency for Research on Cancer (IARC-WHO), 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

[4] Section for Epidemiology, Department of Public Health, Aarhus University, DK-8000, Aarhus, Denmark

[5] Department of Cardiology, Aalborg University Hospital, Fredrik Bajers Vej 5 9100, Aalborg, Denmark

[6] Danish Cancer Society Research Centre, Diet, Genes and Environment, Strandboulevarden 49 DK-2100, Copenhagen, Denmark

[7] Université Paris-Saclay, Univ. Paris-Sud, UVSQ, Inserm, CESP, Generations and health, F-94805, Villejuif, France

[8] Gustave Roussy, F-94805, Villejuif, France

[9] Division of Cancer Epidemiology, German Cancer Research Centre, Im Neuenheimer Feld 280 69120, Heidelberg, Germany

[10] Hellenic Health Foundation, Kaisareias 13 & Alexandroupoleos GR-115 27 Athens, Greece

[11] Bureau of Epidemiologic Research, Academy of Athens, Leoforos Eleftheriou Venizelou 28, 106 79, Athens, Greece

[12] Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, 72-74 Vassilissis Sophias Avenue,115 28, Athens, Greece

[13] Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, 02115 Boston, USA

[14] Department of Clinical Medicine and Surgery, Section of Endocrinology, Federico II University, Via Pansini, 5-80131, Naples, Italy

[15] Epidemiology and Prevention Unit; Fondazione IRCCS National Cancer Institute, via Venezian 1, 20133, Milano, Italy

[16] Cancer Registry and Histopathology Unit, Civic-M.P.Arezzo Hospital, Contrada Rito, 97100, ASP Ragusa, Italy

[17] HuGeF Foundation, Via Nizza 52, 10126 Torino, Italy

[18] Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute ISPO, Via delle Oblate 2, Florence, Italy

[19] Department of Epidemiology, Julius Centre for Health Sciences and Primary Care, University Medical Centre, Heidelberglaan 100, 3584 CX Utrecht, Netherlands

[20] National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9 3721 MA Bilthoven, Netherlands

[21] Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Hansine Hansens veg 18, 9019, Tromsø, Norway

[22] Cancer Registry of Norway – Institute of Population-Based Cancer Research, Ullernchausseen 64, 0379 Oslo, Norway

[23] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 5, 171 65 Solna, Stockholm, Sweden

[24] Genetic Epidemiology Group, Folkhälsan Research Center, Haartmansgatan 8, 00290, Helsinki, Finland

[25] Department of Biobank Research, Umeå University, Förvaltningshuset Universitetstorget 16, 901 87, Umeå, Sweden

[26] Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology, Avda Gran Via 199-203 08908, Barcelona Spain

[27] Public Health Directorate, Ciriaco Miguel Vigil St, 9 33006 Oviedo, Asturias, Spain

[28] Public Health Division of Gipuzkoa-BIODONOSTIA, Basque Regional Health Department, Pº Dr. Beguiristain s/n, 20014 Donostia , San Sebastián Gipuzkoa Spain

[29] Navarre Public Health Institute, Campus de Arrosadia, s/n, 31006 Pamplona, Spain

[30] Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Ronda de Levante 11, 30008, Murcia, Spain

[31] Andalucian School of Public Health, Research Institute Biosanitary Granada, 18080 Cuesta del Observatorio 4 Campus Universitario de Cartuja, Granada, Spain

[32] CIBER Epidemiology and Public Health (CIBERESP), Av. Monforte de Lemos 3-5, 280289, Madrid, Spain

[33] Department of Surgical Sciences, Uppsala University, University Hospital, SE-751 85 Uppsala, Sweden

[34] Department of Odontology, Umeå University, SE 901 87, Umeå, Sweden

[35] Ear Nose and Throat Department, Lund University, Dept of Otorhinolaryngology, University Hospital, SE-205 02, Malmö Sweden

[36] Nutrition Epidemiology Research Group, Department of Clinical Sciences, Lund University, Skåne University Hospital, SE-205 02 Malmö, Sweden

[37]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Roosevelt Drive, OX3 7LF Oxford UK

[38] MRC Epidemiology Unit, University of Cambridge, School of Clinical Medicine, Institute of Metabolic Science, CB2 0SL Cambridge, UK

[39] University of Cambridge, Clinical Gerontology Unit, Addenbrooke's Hospital, Hills Road CB2 2QQ Cambridge, UK

[40] Cancer Research UK/Public Health England, London Road, London, SE1 6LH, UK

Competing Interests: T*h*e authors have no competing interests to declare.

Financial support: The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS), PI13/00061 to Granada; , PI13/01162 to EPIC-Murcia), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of

Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to K.T. Khaw, N.J. Wareham; C570/A16491 to R.C. Travis and C8221/A19170 to Tim Key (EPIC-Oxford), Medical Research Council (1000143 to K.T. Khaw, N.J. Wareham, MR/M012190/1 to Tim Key (EPIC-Oxford)) (United Kingdom).

Abstract

Background

Emerging evidence from cohort studies indicates that adiposity is associated with greater incidence of head and neck cancer (HNC). However, most studies have used self-reported anthropometry which is prone to error.

Methods

Among 363 094 participants in the European Prospective Investigation into Cancer and Nutrition study (EPIC) with measured anthropometry, there were 837 incident cases of HNC. HNC risk was examined in relation to body mass index (BMI) [lean: < 22.5 kg/m^2, normal weight (reference): 22.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, obese: $\geq$ 30 kg/m^2], waist circumference (WC), hip circumference (HC) and waist to hip ratio (WHR) using Cox proportional hazards models.

Results

Among men, a BMI < 22.5 kg/m^2 was associated with higher HNC risk [hazard ratio (HR) 1.62, 95% confidence interval (CI) 1.23 – 2.12)]; BMI was not associated with HNC among women. WC and WHR were associated with greater risk of HNC among women, (WC per 5 cm: HR 1.08, 95% CI 1.02 – 1.15; WHR per 0.1 unit: HR 1.64, 95% CI 1.38 – 1.93). After stratification by smoking status, the association for WHR was present only among smokers ($p_{\text{interaction}}$ 0.004). Among men, WC and WHR were associated with HNC only upon additional adjustment for BMI (WC per 5 cm: HR 1.16, 95% CI 1.07 – 1.26; WHR per 0.1 unit: HR 1.42, 95% CI 1.21 – 1.65).

Conclusion

Central adiposity, particularly among women, may have a stronger association with HNC risk than previously estimated.

Impact

Strategies to reduce obesity may beneficially impact HNC incidence.

Running title: Measured anthropometry and head and neck cancer in EPIC

Keywords: Head and neck cancers, obesity, waist circumference, waist:hip ratio, body mass index, smoking

Word count: 4313

Total number of figures: 1 Main text, 1 Supplementary

Total number of tables: 3 Main text, 3 Supplementary

Introduction

Cancers of the oral cavity, pharynx and larynx (known collectively as head and neck cancers, or HNC) are the sixth most common form of cancers worldwide (1). HNC is positively associated with tobacco (2), alcohol (2) and human papillomavirus (HPV), especially HPV-16 (3). Evidence from case-control studies suggest that adiposity was inversely associated with the risk of HNC (4-12), an observation that was in contrast to the positive association with BMI for other cancer sites, such as breast, oesophagus (adenocarcinoma), endometrium and colon (13-16). Initial results from two prospective studies indicated that BMI classification was not associated with HNC risk (17, 18), but the number of cases in both studies (n < 350) limited the capacity for subgroup analysis. Subsequently, evidence of a divergent association for measures of anthropometry and HNC was reported by a large pooled consortium of twenty cohort studies (19): BMI was inversely associated with HNC risk among current smokers, whereas it was positively associated with HNC risk among non-smokers. Furthermore, greater abdominal obesity (waist circumference or waist to hip ratio) was associated with higher HNC risk in the consortium study, regardless of smoking status (19). These results represent a substantial development in the characterization of anthropometry and HNC. However, the majority of studies in the pooled cohort relied on self-reported measures of anthropometry, which are prone to error (20-22). Greater precision in the estimates of the relationship between anthropometry and HNC could be gained through analysis of those with measured anthropometry.

The aim of the present analysis was to examine the association between measures of general adiposity (BMI), central adiposity (waist circumference, hip circumference and waist to hip ratio) and HNC among participants in the European Prospective Investigation into Cancer and Nutrition (EPIC), further evaluating associations for differences by smoking status. Our analysis also incorporates information on changes in smoking status and weight after baseline, which (to the best of our knowledge) has not previously been included in analyses of anthropometry and HNC risk.

Materials and Methods

General study description

EPIC is a multi-centre prospective cohort study, which recruited 521 448 volunteers from 23 centres in 10 countries (Denmark, France, Germany, Greece, Italy, Norway, the Netherlands, Spain, Sweden, and the United Kingdom) between 1992 and 2000. The study design and population has been described in detail previously (23, 24). In brief, the study included volunteers aged mostly 25 to 70 years at the time of recruitment. Questionnaires on diet, education, occupation, previous illnesses, alcohol, tobacco consumption, and physical activity were completed by participants. The study was approved by all relevant ethical review boards, and all participants provided consent for the retention of acquired data and follow-up for incidence of cancer and death.

Study sample

There were 491 992 eligible participants who had no history of prevalent cancer (except for non-melanoma skin cancer) at baseline and complete information on length of follow-up. Participants were excluded if they had missing measurements of height or weight, waist circumference (WC, centimetres) and hip circumference (HC) (*n*=88,874), self-reported smoking status (*n*=11,696) or baseline alcohol intake (*n*=6,199), or had extreme anthropometric values (height greater than 244 cm or less than 122 cm (*n*=6); BMI less than 15 kg/m^2 (*n*=48) or greater than 60 kg/m^2 (*n*=56); WC less than 40 cm (*n*=0) or greater than 160 cm (*n*=14). In total, 363,094 participants were included in the current analysis.

Follow-up and assessment of HNC

To identify incident cases of HNC and assess vital status of the participants during follow-up data from population-based cancer registries and mortality registries were used, with exception of France, Germany, Greece and Naples (Italy), where a combination of different active follow-up methods were applied. The last date of follow-up varied by EPIC centre, and ranged from June 2008 to December 2013.

We applied the same definition of HNC as used by the INHANCE consortium (2), which consists of five sub-sites identified by the following ICD10 [International Classification of Diseases]-

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 (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, and C10.9), oral cavity, pharynx unspecified or overlapping (C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; 5), hypopharynx (C12.9, C13.0–C13.2, C13.8, and C13.9) and larynx (C32.0–C32.3 and C32.8–C32.9). Tumour stage (I–IV) was based either on the TNM staging (n=169), the categories "localized/metastatic/metastatic regional/metastatic distant" provided by study centres (n=176), or was missing/unknown (n=492).

Assessment of anthropometry

Body weight (kilograms) and height (centimetres) were measured according to standardised procedures without shoes during a clinic visit (25). In the 'Health-conscious' group in the UK, measured data was not available from all participants; instead, self-reported anthropometric data was adjusted using prediction equations derived from a subset of participants for whom both self-reported and measured anthropometric data were available (22). WC was measured at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest according to study centre, except in Norway and Umeå (Sweden), where WC was not measured. HC (centimetres) was measured over the buttocks or at the widest point. To account for between-centre methodological heterogeneity, we subtracted 1.5kg from weight and 2.0cm from waist and hip circumference for participants who were measured while normally dressed. We subtracted 1kg for weight for participants who were measured in light clothing (25).

Data analysis

Hazard ratios (HRs) and 95% confidence intervals (95% CI) for associations between anthropometric measures of adiposity and HNC were estimated using Cox proportional hazard models with age as the time scale (time of entry: age at recruitment, time of exit: age of diagnosis of HNC, loss to follow-up or death, whichever came first). The Cox models were stratified by centre, smoking status, and age at recruitment in 1-year categories. Inspection of Schoenfeld residuals indicated that the proportional hazards assumption was not violated. BMI groups were classified as

follows:<22.5 kg/m^2 (lean), 22.5-24.9 kg/m^2 (normal weight), 25-29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese); this is a modification of the standard World Health Organization BMI cut-points (26) in order to reflect BMI 22.5 – 24.9 kg/m^2 as the lowest mortality risk group (27)

The dose-response relationship was examined by fitting Cox proportional hazards models with restricted cubic splines for BMI, WC, and WHR as continuous variables, adjusted for the same covariates as before analysis. Knots were placed at the 5^{th}, 25^{th}, 75^{th} and 95^{th} percentiles of the anthropometric measurement followed by corresponding likelihood ratio tests comparing the goodness-of-fit of the models with and without the spline terms (28, 29).

Analyses of WC and WHR were conducted with and without inclusion of BMI (continuous) as described by Pischon et al. (30). WC and HC were examined independently and in mutually adjusted models to evaluate the relative contribution of the components of WHR. Wald tests based on cross-product terms were used to examine potential interactions between HNC and BMI (categorical, as described above), WC, HC and WHR across sex, smoking status and alcohol intake [non-drinkers, light drinkers (< 12 g/day) or moderate/heavy drinkers (≥12 g/day)]. We also fitted models separately by HNC sub-sites (oral cavity, oropharynx, hypopharynx, and larynx), in which heterogeneity across sites was assessed by joint Cox proportional hazards models (31). For all models, the potential confounders selected a priori were smoking (current, former, never), education (none/primary school, technical/professional, secondary, longer education, or missing) and baseline alcohol intake [non-drinkers, >0 –6 g/day, >6 –12 g/day, >12-24 g/day, >24 –60 g/day (men) or >24 –36 (women), >60 –96 g/day (men) or >36 g/day (women), > 96 g/day (men)].

Sensitivity analyses were undertaken to explore adjustment for physical activity, fruit and vegetable intake, detailed smoking history [age at smoking initiation, lifetime number of cigarettes per day, current number of cigarettes per day (current smokers), and time since quitting (former smokers)], adjustment for lifetime alcohol intake [never drinkers, past heavy drinkers (women: ≥30g/d women, men ≥60/d; during any past decade starting at age 20), and never heavy drinkers (women: never ≥ 30g/d, men never ≥60g/d)]. In further sensitivity analyses, we excluded the first

three years of follow-up and restricted the analysis to stage I (localized) and stage II (metastatic) cancers in order to reduce the likelihood of including undiagnosed cases with disease-related weight loss at baseline. The impact of changes in smoking status or weight after follow-up was explored in a sub-set of participants from the EPIC-PANACEA study (described in detail elsewhere (32)), from whom self-reported data was collected again two to 11 years after baseline (average 5 years; *n* = 268,185 for the present analysis). For complete correspondence to INHANCE definition of HNC, the analyses were repeated for squamous cell carcinomas only (n= 742 cases). Lastly, the calibrated anthropometric data that was derived from self-reported measures from a subset of Oxford participants (*n* = 40,417, including 44 HNC cases) was excluded to evaluate any impact on associations detected.

All analyses were conducted with SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics

During a median follow-up of 15.1 years, there were 584 incident HNC cases among 126 307 men, and 253 incident HNC cases among 236 787 women. The majority (88.8%) of HNC cases were squamous cell carcinomas. Baseline characteristics are presented in Table 1. Compared to the other BMI groups, lean men and women reported a higher frequency of current smoking, higher education levels and lower mean age, WC, HC, and WHR. Scatterplots of the associations between BMI (kg/m^2) and measures of central adiposity, illustrate a relatively stronger correlation between BMI and WC (Supplementary Figure 1a) compared to BMI and WHR (Supplementary Figure 1b).

Preliminary analyses indicated interactions by sex between HNC risk and WC (*P* value 0.029) and WHR (*P* value 0.006), therefore subsequent analyses were stratified by sex, including BMI (*P* for interaction by sex 0.077). Spline analyses indicated a non-linear association between BMI and HNC among men ($P_{\text{nonlinearity}}$ 0.0011 (Figure 1)); the corresponding *P* value for women was 0.20. There

was no evidence of non-linearity in relation to HNC risk for WC, HC or WHR among men (*P* values 0.060, 0.23, and 0.29 respectively) or women (*P* values 0.55, 0.73, 0.74 respectively).

BMI and HNC

A greater risk of HNC was detected among men with a BMI < 22.5 kg/m^2 (HR 1.62, 95% CI 1.23 – 2.12) compared to the reference category (BMI 22.5 – 24.9 kg/m^2), but no associations were detected among those with relatively higher BMI classification (Table 2). Among women, there were no associations between BMI level and HNC risk (Table 2). Following stratification by smoking status, greater risk of HNC was detected among current smokers with BMI < 22.5 kg/m^2 (for both men and women), and a marginally significant greater risk of HNC was detected among women never smokers with BMI > 30 kg/m^2 (HR 1.90, 95% CI 0.98 – 3.71, *P* value 0.058). However, testing for significant interactions between HNC risk and smoking status yielded null results (*P* values 0.68 and 0.35 among men and women respectively) therefore observed variation between groups must be interpreted with caution.

WC and HNC

WC was not associated with HNC risk among men in the model adjusted for education and alcohol intake (Table 2); however, further adjustment for BMI yielded a positive association (per 5 cm HR 1.16, 95% CI 1.07 – 1.26). In contrast, WC among women was associated with HNC risk independent of adjustment for BMI [per 5 cm HR 1.08 (95% 1.02 – 1.15)]. There was no evidence of an interaction between WC and smoking status in relation to HNC risk for men or women, with or without adjustment for BMI.

WHR and HNC

A marginally positive association was detected by WHR and HNC risk among men (HR per 0.1 unit 1.14, 95% CI 0.99 – 1.30, *P* value 0.07); a stronger association was detected after adjustment for

BMI (Table 2). Among women, WHR was positively associated with HNC risk (HR per 0.1 unit 1.64, 95% CI 1.38 – 1.93); this association was only marginally altered by further adjustment for BMI. A significant interaction between WHR and HNC risk across smoking groups was detected among women (*P* value 0.004) but not men (*P* value 0.63). Each 0.1 unit higher WHR was associated with a more than two-fold higher risk of HNC among female smokers, whereas no association was detected among never or former smokers.

WC, HC, and HNC

WC and HC were both independently associated with HNC risk among men and women, with effects in opposing directions: a higher WC (per 5cm, adjusted for HC) was associated with greater HNC risk (men HR 1.11, 95% CI 1.03-1.19; women HR 1.29, 95% CI 1.18 – 1.41), whereas a higher HC (per 8 cm, adjusted for WC) was associated with lower HNC risk (men HR 0.69, 95% CI 0.59 – 0.82; women HR 0.64, 95 % CI 0.53 – 0.76). There was no evidence of an interaction between WC (adjusted for HC) and smoking status among men or women. In contrast, for HC (adjusted for WC), the interactions in relation to smoking status were significant for women (*P* value 0.0002) and suggestive among men (*P* value 0.07), with relatively stronger effects seen among current smokers. Among men, the results for HC were broadly similar whether or not WC was adjusted for in the analyses. Among women, however, HC without adjustment for WC was not associated with HNC risk overall, with opposing effects observed for never smokers (HR 1.21, 95% CI 1.01 – 1.33) and current smokers (HR 0.68, 95% CI 0.55 – 0.84) (*P* for interaction 0.002).

Subgroup and sensitivity analyses

There was no evidence of heterogeneity across HNC sub-sites (oral, oropharyngeal, hypopharynx, or larynx) in relation to BMI, WC, or WHR among men or women (Table 3). In contrast, there was evidence that the association between HC (adjusted for WC) and lung cancer risk varied by HNC site among women (*P* 0.033), with all HR values significantly below 1. Similarly, tests

for interactions between alcohol intake and BMI, WC, or WHR in relation to HNC risk yielded non-significant values (data not shown). Additional adjustment for details of smoking history [age at smoking initiation, lifetime number of cigarettes per day, current number of cigarettes per day (current smokers), and time since quitting (former smokers)], lifetime alcohol intake, fruit and vegetable intake, physical activity, exclusion of the first three years of follow-up, or restriction to stage I and II cancers (n= 235 cases) did not materially alter the results presented in Table 2 (data not shown). Similarly, additional adjustment for weight gained between baseline and the second questionnaire yielded negligible changes to the results obtained without this information included in the models (Supplementary Table 1). Upon restricting the analysis to those who were never or current smokers at baseline and at the time of the second questionnaire, results for WC, HC and WHR in relation to HNC risk were broadly unchanged among men and women (Supplementary Table 2); as an exception, WC among never smoking men was significantly associated with HNC risk (HR 1.26, 95%CI 1.04 – 1.53). The corresponding analysis for BMI yielded null results for men and women (Supplementary Table 2); however, the reduction in the number of HNC cases per BMI subgroup is noteworthy. Following the exclusion of participants from Oxford with calibrated self-reported anthropometric measurements, there were no material changes to the results obtained for measures of adiposity and HNC among men (Supplementary Table 3). Among women, excluding the calibrated self-reported values yielded more strongly positive associations with HNC risk for those with low BMI (HR 1.58, 95%CI 1.06-2.36), among obese never smokers (HR 2.33, 95% CI 1.10 - 4.93) and among low BMI current smokers (HR 2.22, 95%CI 1.26 – 3.89) (Supplementary Table 3). Similarly, restriction of the analysis to squamous cell carcinomas did not materially change the nature of the results detected (data not shown).

Discussion

In this large, prospective cohort of over 360,000 individuals, greater levels of central adiposity (WC and WHR) were associated with higher risk of HNC among women and men; among men, statistically significant associations for central adiposity were detected only after further

adjustment for BMI. Low BMI (< 22.5 kg/m^2) was associated with greater risk of HNC among men compared to the reference category (22.5-24.9 kg/m^2); stratification by smoking status yielded higher risk among male and female smokers with low BMI. However, caution is required in interpretation of this subgroup analysis due to not having found evidence for a statistically significant interaction between BMI and smoking status in relation to HNC risk. Among women, there was evidence of an interaction between WHR and smoking status in relation to HNC. Stratification by smoking yielded a strong positive association between WHR and HNC risk among current smokers among women; mutual adjustment for WC and HC indicated that this is explained by a relatively stronger protective effect of higher HC, rather than high risk associated with greater WC. The observed associations were not explained by variation in self-reported alcohol or tobacco exposure history. Similarly, the results were not materially changed by excluding the first three years of follow-up, thus reducing the likelihood of cases presenting with disease-related weight loss at baseline. There was no evidence of confounding by other lifestyle factors, including physical activity and fruit and vegetable intake, but the possibility of confounding by unknown or unmeasured factors remains. Therefore, the observed higher HNC incidence for males with low BMI, and female smokers with greater WHR values, requires confirmation in other studies.

Many of our results were consistent with those of the large cohort studies (33, 34) and pooled analysis of anthropometry and HNC (19) (the latter of which included data from an earlier follow-up of the EPIC cohort). The strength of the associations detected for BMI and WHR in relation to HNC risk in the NIH-AARP study, the largest single cohort study to date on this topic, (33) were broadly consistent with those reported in the present study for men; it is likely that their HNC cases were predominantly men, given a higher incidence of HNC among men and the higher proportion of men (60%) in the NIH-AARP cohort (33). As in the present study, the risk of HNC in the Netherlands Cohort Study (NLCS) was significantly higher among those with relatively low BMI values (34). However, further comparison of the results by smoking status is limited as there was no evidence of non-linearity between BMI and HNC risk in NLCS and therefore BMI analysed as a continuous

variable among smoking subgroups. Similar to the present results, the pooled analysis reported that HNC risk was positively associated with WC and WHR and inversely associated with HC (among smokers only) (19), but found no evidence of an interaction across smoking groups in the pooled analysis. Stronger associations were detected for the measured anthropometric data used in the present analysis compared to the pooled analysis. However, the heterogeneity in the association between BMI and HNC by smoking status in the pooled analysis was not replicated in the present study; this may have been due to limited HNC cases in some BMI groups. The pooled consortium study is the largest analysis to date, and comprised predominantly self-reported anthropometric data (including some EPIC centres where only self-reported data was collected). Discrepancies in results between the present and the pooled analysis may be due to factors other than error introduced by self-reported anthropometry; for example, in the consortium analysis adjustment was made for genetic ancestry. However, the impact of misclassification by self-reported anthropometry is well-established, particularly when categories are used as the unit of analysis (22). If central adiposity is positively associated with HNC risk, evidence that self-reported WC and WHR values are lower among those with greater BMI and larger waist size (35, 36) suggests that estimates of self-reported central adiposity and HNC risk may be biased towards the null. Overall, the pooled consortium study provided strong evidence of a positive association between adiposity and HNC, particularly for abdominal obesity and among never smokers, and had a substantial sample size that enabled thorough study of subgroups. The results from the present analysis further support the findings of the pooled analysis and highlight the urgency to implement effective policies to reduce obesity.

A novel observation that emerged from the present analysis was relative strength of association between central adiposity and HNC risk among women compared to men, and the apparent inverse association between HC (adjusted for WC) and HNC risk, particularly among smokers. Previously within the EPIC cohort, WC-adjusted HC has been positively associated with the risk of oesophageal cancer, although no interactions by smoking status were detected (16).

It has been proposed that greater subcutaneous fat storage on the hips may be associated with reduced cancer risk by serving as a "metabolic sink" to prevent lipotoxic effects (37, 38), but this mechanism has not been established. Similarly, as there are no established biological pathways for an association between adiposity and HNC risk, it is difficult to speculate why such effects might differ by sex. Proposed mechanisms for adiposity-cancer associations include insulin and insulin-like growth factors, sex steroids, adipokines and systematic inflammation (39) These proposed pathways are supported by evidence from cohort studies and randomized controlled trials that intentional weight loss is associated with lower levels of oestrogen, oestradiol, inflammatory markers and lower incidence of cancers at a range of sites (40). Mechanistic evidence regarding adiposity and HNC is limited, but includes a small study of laryngeal cancer patients in which higher levels of leptin expression were detected in tumour tissue compared with healthy tissue, and a positive association between leptin expression and cancer recurrence was noted (41). Excess adipose tissue is typically stored centrally for men but gluteofemorally for women (42), therefore the accumulation of central adiposity among women may be indicative of metabolic imbalances (i.e. excess androgens, as noted in polycystic ovarian syndrome (43)) that would not be observed among men. Given the novelty of the present findings, further sex-stratified analysis in other populations is required to confirm that these differences are pervasive in the context of measured anthropometry.

BMI-adjusted central adiposity was associated with HNC in the present analysis, however, we would advise caution in the interpretation of mutually adjusted anthropometric values. WC and WHR are both highly correlated with BMI, and so the interpretation of relative risks for an increment in these variables for a given BMI is not straightforward. That is, for a given fixed BMI the variability in WC and WHR is limited. The adjustment for multiple aspects of anthropometry in relation to HNC is particularly complex within the context of smoking status. BMI is typically lower among current smokers than among former or never smokers (44-47), possibly as a result of decreased appetite (48), higher resting metabolic rate (49-51), or morbid conditions that make them lean. Smokers, despite lower weight, also have a higher WC, lower HC, and higher WHR values than non-smokers on

average (52). These differences are more pronounced among smokers with relatively greater smoking intensity and former smokers with comparatively shorter duration since quitting, and are not attenuated by adjustment for physical activity, energy intake, alcohol intake, and education (46). Possible explanations for these differences are proposed estrogenic effects of smoking (53), or uncontrolled confounding for self-reported factors that are prone to error (e.g. lower HC among current smokers could reflect lower physical activity and consequent muscle wasting in the gluteal region).

Strengths of the present study include the prospective design, availability of measured anthropometry, wide range of exposure values, and large sample size that enabled stratification by smoking status. The availability of detailed data on past smoking habits and alcohol intake facilitated thorough evaluation for potential confounding through these exposures. However, the study has also some limitations. First, there were a relatively small number of cases in some BMI groups in the analyses run separately by smoking status and by HNC site, particularly among never smokers and for cancers of the hypopharynx; the power for related interaction tests may have been limited, particularly among women. Further, there is uncertainty as to what the most appropriate reference category and classification system ought to be applied to BMI: the present analysis combined all individuals with BMI < 22.5 kg/m^2, using 22.5-24.9 kg/m^2 as the reference group. The WHO classification system identifies those with BMI < 18.5 kg/m^2 as underweight, therefore we may have reduced our ability to detect associations between underweight and HNC by setting our lowest category as 15.0 – 22.5 kg/m^2. However, there was a limited number of participants with measured BMI < 18.5 kg/m^2 (n=4604, including six male and four female HNC cases) therefore the impact of combining underweight and low-normal weight individuals in the present study is unlikely to have been substantial. The spline analysis indicated that the BMI values with the lowest risk of HNC may differ for men and women, as does the magnitude of risk associated with relatively lower BMI values; further research is needed to confirm and characterize these differences by sex. Lastly, the use of measured anthropometry in the present study yielded larger effect sizes than seen in previous

research where self-report has been used, and we propose that this discrepancy may be due to the error that is known to exist for self-report. However, this cannot be confirmed in the absence of both measured and self-reported data on the same subjects. We could not undertake such a comparison as the majority of EPIC participants had measured anthropometry only, with only 12% of the present sample having both measured and self-reported values.

Summary

The present analysis yielded evidence of a positive association between central adiposity and HNC, particularly among women, with larger effect sizes detected than in previous studies using self-reported anthropometry. If a causal association exists between adiposity and HNC, the increases in global obesity prevalence observed over time (54) may also result in higher incidence of HNC. In addition to continued emphasis on smoking cessation, efforts to address the prevalence of obesity may therefore contribute to lower incidence of HNC.

Acknowledgements:

Data sharing: For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

References

(1) Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *Ca-A Cancer Journal for Clinicians* 2005;**55**:74-108.

(2) Hashibe M, Brennan P, Benhamou S, Castellsague X, Chu C, Curado MP, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: Pooled analysis in the international head and neck cancer epidemiology consortium. *Journal of the National Cancer Institute* 2007;**99**:777-89.

(3) Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncology* 2010;**11**:781-9.

(4) D'Avanzo B, La VC, Talamini R, Franceschi S. Anthropometric measures and risk of cancers of the upper digestive and respiratory tract. *Nutr Cancer* 1996;**26**:219-27.

(5) Franceschi S, Dal ML, Levi F, Conti E, Talamini R, La VC. Leanness as early marker of cancer of the oral cavity and pharynx. *Ann Oncol* 2001;**12**:331-6.

(6) Garavello W, Randi G, Bosetti C, Dal ML, Negri E, Barzan L, et al. Body size and laryngeal cancer risk. *Ann Oncol* 2006;**17**:1459-63.

(7) Kabat GC, Chang CJ, Wynder EL. The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer. *Int J Epidemiol* 1994;**23**:1137-44.

(8) Kreimer AR, Randi G, Herrero R, Castellsague X, La VC, Franceschi S. Diet and body mass, and oral and oropharyngeal squamous cell carcinomas: analysis from the IARC multinational case-control study. *Int J Cancer* 2006;**118**:2293-7.

(9) Nieto A, Sanchez MJ, Martinez C, Castellsague X, Quintana MJ, Bosch X, et al. Lifetime body mass index and risk of oral cavity and oropharyngeal cancer by smoking and drinking habits. *Br J Cancer* 2003;**89**:1667-71.

(10) Radoi L, Paget-Bailly S, Cyr D, Papadopoulos A, Guida F, Tarnaud C, et al. Body mass index, body mass change, and risk of oral cavity cancer: results of a large population-based case-control study, the ICARE study. *Cancer Causes Control* 2013;**24**:1437-48.

(11) Rodriguez T, Altieri A, Chatenoud L, Gallus S, Bosetti C, Negri E, et al. Risk factors for oral and pharyngeal cancer in young adults. *Oral Oncol* 2004;**40**:207-13.

(12) Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J, et al. 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. *Int J Epidemiol* 2010;**39**:1091-102.

(13) Steffen A, Schulze MB, Pischon T, Dietrich T, Molina E, Chirlaque MD, et al. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:2079-89.

(14) Wolin KY, Carson K, Colditz GA. Obesity and Cancer. *Oncologist* 2010;**15**:556-65.

(15) World Cancer Research Fund/ American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AIRC; 2007.

(16) Steffen A, Huerta JM, Weiderpass E, Bueno-de-Mesquita HB, May AM, Siersema PD, et al. General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2015;**137**:646-57.

(17) Gaudet MM, Patel AV, Sun J, Hildebrand JS, McCullough ML, Chen AY, et al. Prospective Studies of Body Mass Index with Head and Neck Cancer Incidence and Mortality. *Cancer Epidemiol Biomarkers Prev* 2012;**21**:497-503.

(18) Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the prostate, lung, colorectal, and ovarian (PLCO) cohort. *Head Neck* 2013;**35**:914-22.

(19) Gaudet MM, Kitahara CM, Newton CC, Bernstein L, Reynolds P, Weiderpass E, et al. Anthropometry and head and neck cancer:a pooled analysis of cohort data. *Int J Epidemiol* 2015;**44**:673-81.

(20) Kuczmarski MF, Kuczmarski RJ, Najjar M. Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Am Diet Assoc* 2001;**101**:28-34.

(21) Rowland ML. Self-reported weight and height. *Am J Clin Nutr* 1990;**52**:1125-33.

(22) Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. *Public Health Nutr* 2002;**5**:561-5.

(23) Riboli E, Kaaks R. The EPIC project: Rationale and study design. *International Journal of Epidemiology* 1997;**26**:S6-S14.

(24) Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;**5**:1113-24.

(25) Haftenberger M, Lahmann PH, Panico S, Gonzalez CA, Seidell JC, Boeing H, et al. Overweight, obesity and fat distribution in 50-to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutrition* 2002;**5**:1147-62.

(26) World Health Organization. Obesity: Preventing and managing the global epidemic. Geneva: World Health Organization; 2000. Report No.: Technical Report Series no. 894.

(27) Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;**373**:1083-96.

(28) Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst* 1988;**80**:1198-202.

(29) Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed* 1997;**54**:201-8.

(30) Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;**359**:2105-20.

(31) Xue X, Kim MY, Gaudet MM, Park Y, Heo M, Hollenbeck AR, et al. A comparison of the polytomous logistic regression and joint cox proportional hazards models for evaluating multiple disease subtypes in prospective cohort studies. *Cancer Epidemiol Biomarkers Prev* 2013;**22**:275-85.

(32) Vergnaud AC, Norat T, Romaguera D, Mouw T, May AM, Travier N, et al. Meat consumption and prospective weight change in participants of the EPIC-PANACEA study. *American Journal of Clinical Nutrition* 2010;**92**:398-407.

(33) Etemadi A, O'Doherty MG, Freedman ND, Hollenbeck AR, Dawsey SM, Abnet CC. A prospective cohort study of body size and risk of head and neck cancers in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev* 2014;**23**:2422-9.

(34) Maasland DH, van den Brandt PA, Kremer B, Schouten LJ. Body mass index and risk of subtypes of head-neck cancer: the Netherlands Cohort Study. *Sci Rep* 2015;**5**:17744.

(35) Bigaard J, Spanggaard I, Thomsen BL, Overvad K, Tjonneland A. Self-reported and technician-measured waist circumferences differ in middle-aged men and women. *Journal of Nutrition* 2005;**135**:2263-70.

(36) Spencer EA, Roddam AW, Key TJ. Accuracy of self-reported waist and hip measurements in 4492 EPIC-Oxford participants. *Public Health Nutrition* 2004;**7**:723-7.

(37) Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002;**45**:1201-10.

(38) Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond)* 2010;**34**:949-59.

(39) Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer* 2015;**15**:484-98.

(40) Byers T, Sedjo RL. Does intentional weight loss reduce cancer risk? *Diabetes Obes Metab* 2011;**13**:1063-72.

(41) Gallina S, Sireci F, Lorusso F, Di Benedetto DV, Speciale R, Marchese D, et al. The immunohistochemical peptidergic expression of leptin is associated with recurrence of malignancy in laryngeal squamous cell carcinoma. *Acta Otorhinolaryngol Ital* 2015;**35**:15-22.

(42) Geer EB, Shen W. Gender Differences in Insulin Resistance, Body Composition, and Energy Balance. *Gender Medicine* 2009;**6**:60-75.

(43) Escobar-Morreale HF, Millan JLS. Abdominal adiposity and the polycystic ovary syndrome. *Trends in Endocrinology and Metabolism* 2007;**18**:266-72.

(44) Akbartabartoori M, Lean ME, Hankey CR. Relationships between cigarette smoking, body size and body shape. *Int J Obes (Lond)* 2005;**29**:236-43.

(45) Bamia C, Trichopoulou A, Lenas D, Trichopoulos D. Tobacco smoking in relation to body fat mass and distribution in a general population sample. *Int J Obes Relat Metab Disord* 2004;**28**:1091-6.

(46) Canoy D, Wareham N, Luben R, Welch A, Bingham S, Day N, et al. Cigarette smoking and fat distribution in 21,828 British men and women: a population-based study. *Obes Res* 2005;**13**:1466-75.

(47) Molarius A, Seidell JC, Kuulasmaa K, Dobson AJ, Sans S. Smoking and relative body weight: an international perspective from the WHO MONICA Project. *J Epidemiol Community Health* 1997;**51**:252-60.

(48) Mineur YS, Abizaid A, Rao Y, Salas R, DiLeone RJ, Gundisch D, et al. Nicotine decreases food intake through activation of POMC neurons. *Science* 2011;**332**:1330-2.

(49) Moffatt RJ, Owens SG. Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. *Metabolism* 1991;**40**:465-70.

(50) Perkins KA, Epstein LH, Stiller RL, Marks BL, Jacob RG. Acute effects of nicotine on resting metabolic rate in cigarette smokers. *Am J Clin Nutr* 1989;**50**:545-50.

(51) Walker JF, Kane CJ. Effects of body mass on nicotine-induced thermogenesis and catecholamine release in male smokers. *Sheng Li Xue Bao* 2002;**54**:405-10.

(52) Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. *Am J Clin Nutr* 2008;**87**:801-9.

(53) Brand JS, Chan MF, Dowsett M, Folkerd E, Wareham NJ, Luben RN, et al. Cigarette smoking and endogenous sex hormones in postmenopausal women. *J Clin Endocrinol Metab* 2011;**96**:3184-92.

(54) Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet* 2011;**378**:804-14.

Table 1: Baseline demographic, anthropometric and lifestyle characteristics by sex and BMI group in the EPIC study

	Men [a] BMI (kg/m^2)				Women [a] BMI (kg/m^2)			
	<22.5 (n=13 700)	22.5-24.9 (n=29 353)	25-29.9 (n=62 510)	≥30 (n=20 744)	<22.5 (n=65 653)	22.5-24.9 (n=59 548)	25-29.9 (n=74 972)	≥30 (n=36 614)
Age at recruitment(years)	50.1 (12.2)	52.5 (10.1)	53.7 (9.0)	54.1 (8.6)	47.6 (11.3)	51.0 (10.3)	53.3 (9.6)	54.3 (9.2)
Follow-up (years)	13.9 (4.5)	13.9 (4.4)	13.7 (4.4)	13.1 (4.6)	14.3 (3.9)	14.3 (3.9)	14.1 (4.0)	13.8 (4.1)
WC (cm)	81.3 (5.7)	88.0 (5.3)	96.3 (6.2)	109.1 (8.1)	69.8 (5.3)	76.2 (5.7)	84.1 (7.0)	97.8 (9.7)
HC (cm)	92.9 (4.5)	96.9 (4.2)	101.6 (4.7)	109.7 (6.7)	92.7 (4.8)	98.0 (4.6)	103.9 (5.3)	115.4 (8.6)
WHR	0.88 (0.05)	0.91 (0.05)	0.95 (0.05)	1.00 (0.06)	0.75 (0.06)	0.78 (0.06)	0.81 (0.07)	0.85 (0.07)
Smoking status (%)								
Never	36.2	33.4	29.4	26.3	53.8	53.4	58.0	65.8
Former	25.6	34.6	40.8	43.5	23.1	24.9	22.8	19.4
Current	38.2	32.1	29.8	30.2	23.1	21.7	19.2	14.8
Alcohol intake, g/d (%)								
Non drinker	7.2	6.0	6.8	8.5	10.0	12.9	19.5	30.1
>0-6(M)/>0-3(W)	25.7	21.6	19.9	20.6	28.7	27.8	29.3	32.7
>6-12 (M)/>3-12 (W)	17.4	17.2	16.0	14.6	33.5	32.1	28.9	23.1
>12-24	21.4	23.2	22.3	19.5	17.0	16.7	13.6	8.6
>24-60 (M)/> 24-36(W)	22.5	26.1	27.6	26.4	6.8	6.4	5.1	3.2
>60-96 (M)/>36 (W)	4.6	5.0	6.1	7.8	4.0	4.1	3.5	2.4
>96 (M)	1.3	1.0	1.4	2.6				
Education (%)								
Missing	3.2	2.5	2.0	1.7	4.4	4.4	4.0	3.5
Primary school completed	22.2	26.5	37.0	49.8	15.7	26.4	42.0	58.2
Technical/professional school	24.9	25.0	25.1	22.3	24.5	26.3	24.0	19.2
Secondary school	14.8	13.2	10.8	8.7	22.3	19.2	14.6	9.9
Longer education (incl. University degree)	35.0	32.8	25.1	17.5	33.2	23.6	15.4	9.2

[a] Data are mean (SD) unless otherwise specified. (M) = men, (W) = women

Table 2: Measures of adiposity and the risk of HNC among EPIC participants, by smoking status

	All participants		Never		Former		Current		
	n cases	HR (95% CI) [a]	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	$P_{interaction}$ smoking status
Men									
BMI									
<22.5 kg/m^2	93	1.62 (1.23 – 2.12)	7	1.22 (0.48 – 3.09)	13	1.41 (0.73 – 2.73)	73	1.70 (1.24 – 2.34)	0.68
22.5-24.9 kg/m^2	130	1.0 (ref)	13	1.0 (ref)	30	1.0 (ref)	87	1.0 (ref)	
25-29.9 kg/m^2	270	0.92 (0.75 – 1.15)	28	1.22 (0.62 – 2.39)	86	1.00 (0.66 – 1.53)	156	0.85 (0.65 – 1.12)	
≥30 kg/m^2	91	0.88 (0.67 – 1.17)	8	1.14 (0.46 – 2.82)	31	1.04 (0.62 – 1.75)	52	0.78 (0.55 – 1.12)	
WC (per 5 cm)	584	0.98 (0.94 - 1.02)	56	0.94 (0.81 – 1.09)	160	1.03 (0.95 – 1.12)	368	0.96 (0.91 – 1.01)	0.29
WC (per 5 cm) + BMI		1.16 (1.07 – 1.26)		1.12 (0.95 – 1.33)		1.23 (1.10 – 1.37)		1.14 (1.04 – 1.25)	0.31
WHR (per 0.1 unit)	584	1.14 (0.99 – 1.30)	56	0.91 (0.57 – 1.45)	160	1.16 (0.89 – 1.51)	368	1.16 (0.98 – 1.38)	0.63
WHR (per 0.1 unit) + BMI		1.42 (1.21 – 1.65)		1.16 (0.72 – 1.88)		1.42 (1.09 – 1.84)		1.45 (1.21 – 1.74)	0.68
HC (per 8 cm)	584	0.84 (0.76 - 0.93)	56	0.85 (0.60 - 1.20)	160	1.01(0.83 - 1.21)	368	0.77 (0.68 - 0.88)	0.077
WC (per 5 cm) + HC	584	1.11 (1.03 – 1.19)	56	1.06 (0.91 – 1.25)	160	1.17 (1.06 – 1.30)	368	1.09 (1.01 – 1.18)	0.29
HC (per 8 cm) + WC	584	0.69 (0.59 – 0.82)	56	0.83 (0.67 – 1.05)	160	0.83 (0.67 – 1.05)	368	0.64 (0.54 – 0.76)	0.070
Women									
BMI									
<22.5 kg/m^2	68	1.34 (0.94 – 1.93)	15	1.08 (0.53 – 2.21)	11	0.88 (0.40 – 1.93)	42	1.78 (1.06 – 2.97)	0.35
22.5-24.9 kg/m^2	55	1.0 (ref)	16	1.0 (ref)	15	1.0 (ref)	24	1.0 (ref)	
25-29.9 kg/m^2	89	1.26 (0.89 – 1.78)	31	1.25 (0.68 – 2.30)	22	1.02 (0.52 – 1.99)	36	1.45 (0.86 – 2.45)	
≥30 kg/m^2	41	1.37 (0.90 – 2.10)	23	1.91 (0.98 – 3.72)	8	0.99 (0.41 – 2.38)	10	1.03 (0.48 – 2.20)	
WC (per 5 cm)	253	1.08 (1.02 – 1.15)	85	1.12 (1.01 –1.23)	56	1.04 (0.91 – 1.18)	112	1.08 (0.99 – 1.18)	0.66
WC (per 5 cm) + BMI		1.31 (1.18 – 1.46)		1.36 (1.19 – 1.56)		1.25 (1.06 – 1.47)		1.30 (1.15 – 1.48)	0.61
WHR (per 0.1 unit)	253	1.64 (1.38 – 1.93)	85	1.21 (0.87 – 1.69)	56	1.13 (0.73 – 1.73)	112	2.09 (1.70 – 2.56)	0.004
WHR (per 0.1 unit) + BMI		1.75 (1.47 – 2.08)		1.31 (0.93 – 1.83)		1.22 (0.79 – 1.90)		2.19 (1.78 – 2.70)	0.006
HC (per 8 cm)	253	0.94 (0.83 - 1.06)	85	1.21 (1.01 - 1.46)	56	1.03 (0.80 - 1.33)	112	0.68 (0.55 - 0.84)	0.002
WC (per 5 cm) + HC	253	1.29 (1.18 – 1.41)	85	1.34 (1.19 – 1.52)	56	1.24 (1.07 – 1.44)	112	1.28 (1.15 – 1.43)	0.63
HC (per 8 cm) + WC	253	0.64 (0.53 – 0.76)	85	0.70 (0.53 – 0.93)	56	0.70 (0.53 – 0.93)	112	0.48 (0.39 – 0.60)	0.0002

[a] Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake
[b] Cox regression models stratified by age, sex, centre, adjusted for education and alcohol intake

Table 3: Measures of adiposity and the risk of HNC among EPIC participants, by HNC site [a]

	Oral cancer		Oropharyngeal cancer		Hypopharynx		Larynx		$P_{heterogeneity}$ HNC site
	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	
Men									
BMI									
<22.5 kg/m^2	20	1.96 (1.06 – 3.60)	23	1.70 (1.00 – 2.91)	6	0.68 (0.26 - 1.77)	37	1.68 (1.10 - 2.57)	0.56
22.5-24.9 kg/m^2	21	1.0 (ref)	31	1.0 (ref)	17	1.0 (ref)	55	1.0 (ref)	
25-29.9 kg/m^2	54	1.15 (0.66 – 1.95)	68	1.09 (0.70 – 1.68)	23	0.61 (0.33 - 1.15)	115	0.87 (0.63 - 1.21)	
≥30 kg/m^2	19	1.12 (0.58 – 2.13)	14	0.69 (0.36 – 1.30)	8	0.68 (0.28 - 1.67)	45	0.91 (0.60 - 1.36)	
WC (per 5 cm)	114	1.00 (0.91 - 1.10)	136	0.94 (0.86 – 1.03)	54	1.03 (0.88 - 1.20)	252	0.98 (0.92 - 1.05)	0.72
WC (per 5 cm) + BMI	114	1.21 (1.07 – 1.36)	136	1.13 (1.00 – 1.27)	54	1.24 (1.03 - 1.49)	252	1.18 (1.06 - 1.30)	0.73
WHR (per 0.1 unit)	114	1.26 (0.96 – 1.65)	136	1.00 (0.76 – 1.31)	54	1.42 (0.86 - 2.35)	252	1.12 (0.91 - 1.37)	0.56
WHR (per 0.1 unit) + BMI	114	1.60 (1.23 – 2.07)	136	1.28 (0.95 – 1.72)	54	1.79 (1.07 - 2.99)	252	1.39 (1.14- 1.68)	0.53
HC (per 8 cm)	114	0.87 (0.68 - 1.11)	136	0.82 (0.65 - 1.02)	54	0.83 (0.57 - 1.20)	252	0.85 (0.74 - 0.98)	0.98
WC (per 5 cm) + HC	114	1.14 (1.02 – 1.27)	136	1.07 (0.97 – 1.18)	54	1.16 (0.98 - 1.37)	252	1.11 (1.02 - 1.21)	0.73
HC (per 8 cm) + WC	114	0.72 (0.55 – 0.94)	136	0.67 (0.52 – 0.87)	54	0.68 (0.46 - 1.01)	252	0.70 (0.59 - 0.84)	0.98
Women									
BMI									
<22.5 kg/m^2	23	1.05 (0.60 – 1.84)	20	1.56 (0.74 – 3.25)	3	3.09 (0.33 - 28.87)	14	1.27 (0.56 - 2.85)	0.10 [c]
22.5-24.9 kg/m^2	26	1.0 (ref)	12	1.0 (ref)	1	1.0 (ref)	13	1.0 (ref)	
25-29.9 kg/m^2	27	0.75 (0.43 – 1.30)	30	2.09 (1.08 – 4.02)	5	5.73 (0.59 - 55.66)	18	1.15 (0.57 - 2.32)	
≥30 kg/m^2	23	1.42 (0.79 – 2.54)	11	2.03 (0.88 – 4.65)	0	n/a	4	0.60 (0.20 - 1.85)	
WC (per 5 cm)	99	1.13 (1.02 – 1.24)	73	1.14 (1.04 – 1.24)	9	1.01 (0.77 - 1.34)	49	1.04 (0.94 - 1.16)	0.56
WC (per 5 cm) + BMI	99	1.40 (1.22 – 1.61)		1.42 (1.25 – 1.61)	9	1.25 (0.92 - 1.72)	49	1.30 (1.11 - 1.51)	0.57

WHR (per 0.1 unit)	99	1.72 (1.24 – 2.38)	73	1.68 (1.32 – 2.15)	9	2.00 (0.68 - 5.94)	49	1.71 (1.26 - 2.31)	0.99
WHR (per 0.1 unit) + BMI	99	1.86 (1.33 – 2.59)	73	1.77 (1.40 – 2.23)	9	2.20 (0.73 - 6.61)	49	1.79 (1.35 - 2.37)	0.97
HC (per 8 cm)	99	1.06 (0.87 - 1.29)	73	1.04 (0.85 - 1.26)	9	0.66 (0.47 - 0.91)	49	0.79 (0.58 - 1.09)	0.042
WC (per 5 cm) + HC	99	1.35 (1.19 – 1.53)	73	1.35 (1.20 – 1.52)	9	1.21 (0.90 - 1.64)	49	1.24 (1.08 - 1.41)	0.56
HC (per 8 cm) + WC	99	0.70 (0.55 – 0.89)	73	0.69 (0.55 – 0.87)	9	0.43 (0.31 - 0.61)	49	0.54 (0.41 - 0.71)	0.033

[a] HNC site was defined as oro/hypopharynx not otherwise specified among 23 women and 28 men

[b] Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

[c] Among women, the test for interaction between BMI classification and tumour site excluded hypopharynx due to the absence of any cases of hypopharyngeal cancer among BMI 25 – 29.9 kg/m2

Figure Legends:

Figure 1. Restricted cubic spline analysis of the association between measured BMI and the risk of HNC among men (Fig 1a) and women (Fig 1b) in EPIC; knots at the 5^{th}, 25^{th}, 75^{th} and 95^{th} percentiles of BMI, and models adjusted for education, alcohol intake, and smoking.

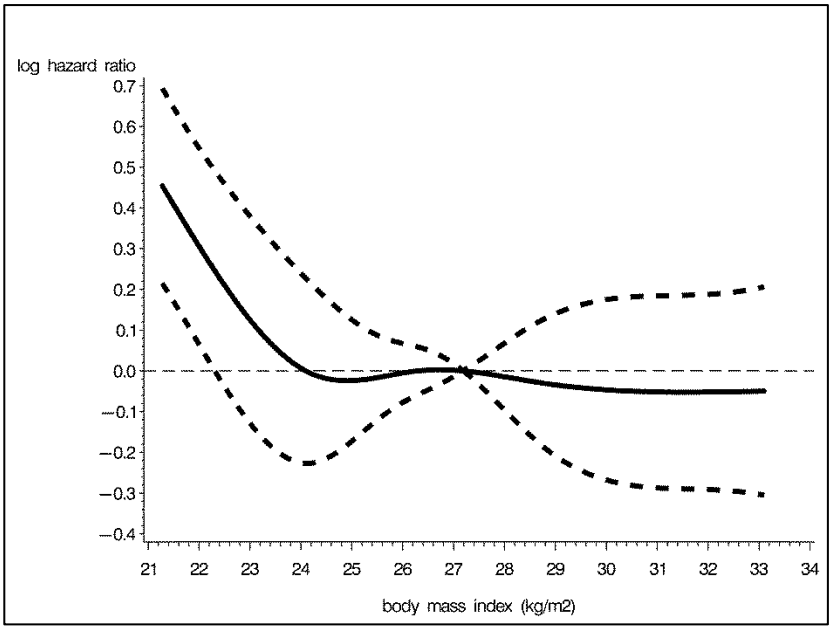


Figure 1a

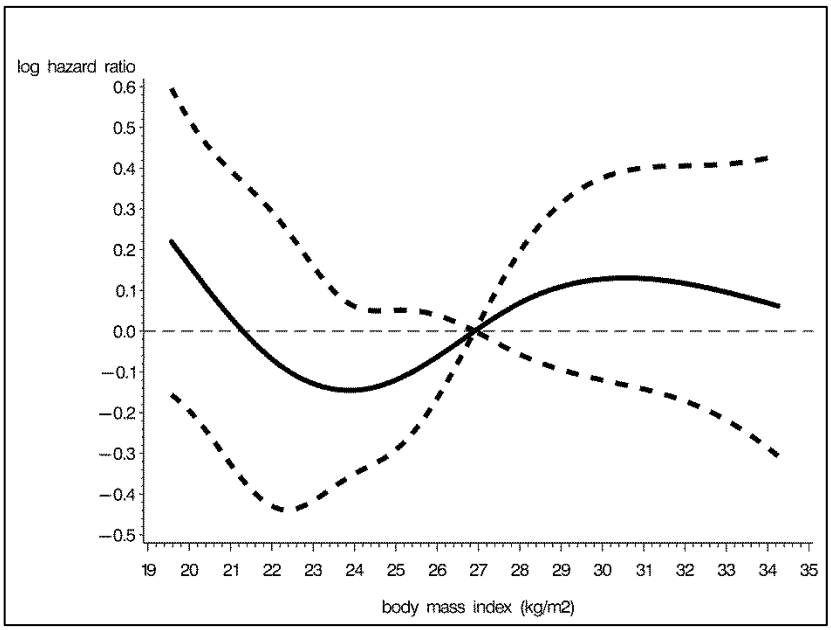


Figure 1b

Figure 1.

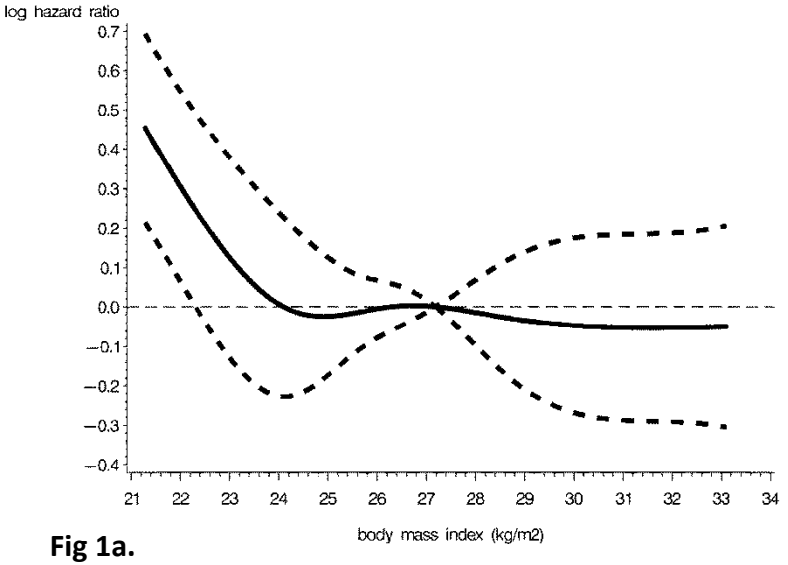


Fig 1a.

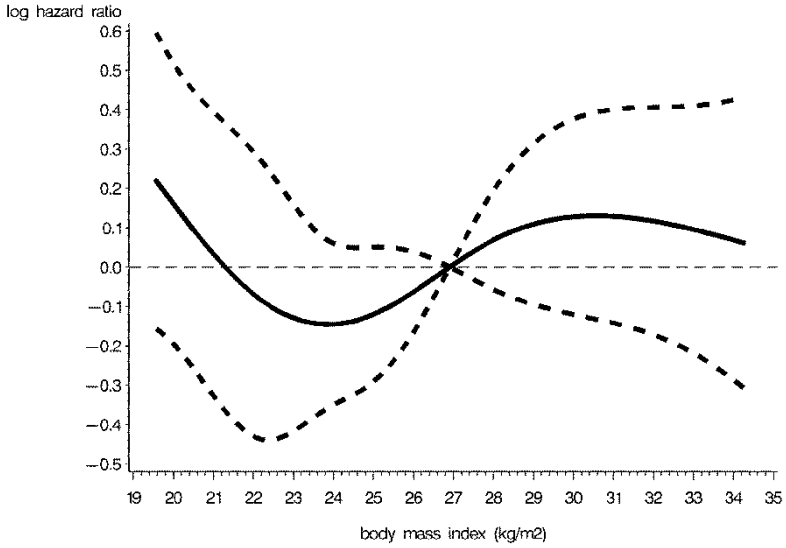
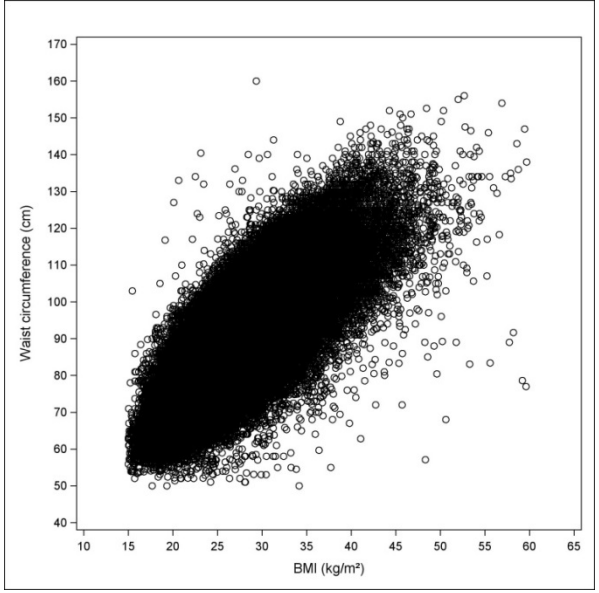
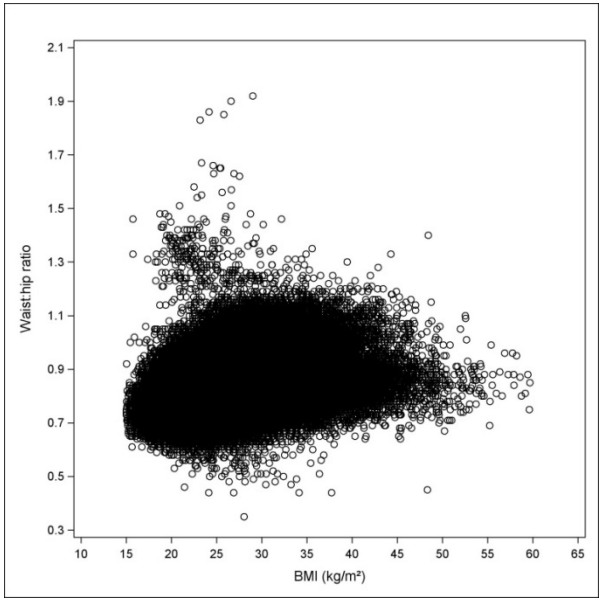


Fig 1b.

Figure 1. Restricted cubic spline analysis of the association between measured BMI and the risk of HNC among men (Fig 1a) and women (Fig 1b) in EPIC; knots at the 5th, 25th, 75th and 95th percentiles of BMI, and models adjusted for education, alcohol intake, and smoking.



Supplementary Fig 1a



Supplementary Fig 1b

Supplementary Figure 1: Scatterplots of the associations between BMI (kg/m2) and WC (Fig 1a) and between BMI (kg/m2) and WHR (Fig 1b).

Supplementary Table 1: Measures of adiposity and the risk of HNC among EPIC participants, including adjustment for weight change after baseline

	Men			**Women**		
	n cases	Model 1 [a]	Model 2 [b]	n cases	Model 1 [a]	Model 2 [b]
Baseline BMI						
<22.5 kg/m^2	51	1.59 (1.10 – 2.29)	1.64 (1.13 – 2.37)	38	1.17 (0.73 – 1.86)	1.18 (0.74 – 1.88)
22.5-24.9 kg/m^2	69	1.0 (reference)	1.0 (reference)	37	1.0 (reference)	1.0 (reference)
25-29.9 kg/m^2	174	1.11 (0.84 – 1.48)	1.07 (0.80 – 1.42)	51	1.13 (0.74 – 1.75)	1.11 (0.72 – 1.71)
≥30 kg/m^2	54	1.01 (0.70 – 1.48)	0.90 (0.62 – 1.32)	22	1.14 (0.66 – 2.00)	1.05 (0.60 – 1.86)
Smoking status						
Never						
Baseline BMI						
<22.5 kg/m^2	4	0.88 (0.26 – 2.91)	0.90 (0.27 – 3.00)	9	0.80 (0.33 – 1.89)	0.80 (0.33 – 1.89)
22.5-24.9 kg/m^2	9	1.0 (reference)	1.0 (reference)	13	1.0 (reference)	1.0 (reference)
25-29.9 kg/m^2	19	1.31 (0.58 – 2.97)	1.24 (0.55 – 2.81)	19	0.96 (0.47 – 1.98)	0.95 (0.46 – 1.96)
≥30 kg/m^2	7	1.60 (0.57 – 4.50)	1.36 (0.48 – 3.90)	13	1.34 (0.59 – 3.03)	1.25 (0.54 – 2.89)
Former						
Baseline BMI						
<22.5 kg/m^2	9	2.05 (0.88 – 4.78)	2.11 (0.91 – 4.93)	4	0.50 (0.15 – 1.64)	0.51 (0.16 – 1.66)
22.5-24.9 kg/m^2	14	1.0 (reference)	1.0 (reference)	10	1.0 (reference)	1.0 (reference)
25-29.9 kg/m^2	57	1.54 (0.85 – 2.79)	1.48 (0.82 – 2.68)	16	1.35 (0.60 – 3.03)	1.31 (0.58 – 2.95)
≥30 kg/m^2	16	1.44 (0.69 – 3.02)	1.31 (0.62 – 2.78)	4	0.90 (0.28 – 2.96)	0.79 (0.24 – 2.59)
Current						
Baseline BMI						
<22.5 kg/m^2	38	1.56 (1.01 – 2.43)	1.62 (1.04 – 2.52)	25	2.01 (1.01 – 3.99)	2.06 (1.04 – 4.10)
22.5-24.9 kg/m^2	46	1.0 (reference)	1.0 (reference)	14	1.0 (reference)	1.0 (reference)
25-29.9 kg/m^2	98	0.94 (0.65 – 1.35)	0.90 (0.63 – 1.30)	16	1.21 (0.58 – 2.54)	1.18 (0.57 – 2.48)
≥30 kg/m^2	31	0.82 (0.50 – 1.33)	0.72 (0.44 – 1.19)	5	0.90 (0.31 – 2.68)	0.81 (0.27 – 2.45)
Interaction by smoking status:		0.60	0.55		0.21	0.21

[a] Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

[b] Same covariates as model 1, further adjusted for self-reported difference in weight over time (kg/year)

Supplementary Table 2: Measures of adiposity and the risk of HNC among EPIC participants, by smoking status at baseline and second questionnaire

		Never smokers, baseline and second [a] questionnaire		Current smokers, baseline and second [a] questionnaire
	n cases	HR (95% CI)	n cases	HR (95% CI)
Men				
Baseline BMI				
<22.5 kg/m^2	5	1.69 (0.53 – 5.42)	30	1.51 (0.93 – 2.45)
22.5-24.9 kg/m^2	7	1.0 (ref)	40	1.0 (ref)
25-29.9 kg/m^2	20	1.74 (0.73 – 4.18)	80	0.89 (0.60 – 1.32)
≥30 kg/m^2	7	2.23 (0.76 – 6.57)	24	0.70 (0.40 – 1.20)
WC (per 5 cm)	39	1.13 (0.96 – 1.33)	174	0.97 (0.89 – 1.05)
WHR (per 0.1 unit)	39	1.22 (0.69 – 2.15)	174	1.14 (0.88 – 1.48)
HC (per 8 cm)	39	1.32 (0.91 - 1.90)	174	0.80 (0.67 - 0.97)
WC (per 5 cm) + HC	39	1.26 (1.04 – 1.53)	174	1.08 (0.96 – 1.23)
HC (per 8 cm) + WC	39	1.09 (0.71 – 1.67)	174	0.67 (0.51 – 0.88)
Women				
Baseline BMI				
<22.5 kg/m^2	10	1.22 (0.50 – 2.98)	21	1.91 (0.90 – 4.09)
22.5-24.9 kg/m^2	10	1.0 (ref)	11	1.0 (ref)
25-29.9 kg/m^2	21	1.32 (0.61 – 2.86)	16	1.38 (0.62 – 3.05)
≥30 kg/m^2	15	1.94 (0.83 – 4.51)	6	1.45 (0.50 -4 .21)
WC (per 5 cm)	56	1.11 (0.98 – 1.26)	54	1.06 (0.93 – 1.20)
WHR (per 0.1 unit)	56	1.14 (0.74 – 1.76)	54	1.91 (1.37 – 2.66)
HC (per 8 cm)	56	1.23 (0.98 - 1.56)	54	0.73 (0.54 - 0.98)
WC (per 5 cm) + HC	56	1.28 (1.08 – 1.51)	54	1.21 (1.03 – 1.43)
HC (per 8 cm) + WC	56	0.88 (0.65 – 1.21)	54	0.52 (0.37 – 0.74)

[a] Second questionnaire completed on average 5 years after baseline

[b] Cox regression models stratified by age and centre; adjusted for education and alcohol intake

Supplementary Table 3: Measures of adiposity and the risk of HNC in the EPIC study, excluding Oxford participants with calibrated self-reported anthropometry

	All participants		Never		Former		Current		
	n cases	HR (95% CI) [a]	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	n cases	HR (95% CI) [b]	*p* for interaction by smoking status
Men									
BMI									
<22.5 kg/m^2	90	1.68 (1.27 – 2.21)	6	1.45 (0.53 – 4.00)	13	1.58 (0.81 – 3.07)	71	1.68 (1.22 – 2.32)	0.88
22.5-24.9 kg/m^2	125	1.0 (ref)	11	1.0 (ref)	28	1.0 (ref)	86	1.0 (ref)	
25-29.9 kg/m^2	264	0.93 (0.75 – 1.15)	24	1.16 (0.56 – 2.41)	84	1.06 (0.69 – 1.64)	156	0.86 (0.65 – 1.13)	
≥30 kg/m^2	91	0.90 (0.68 – 1.19)	8	1.22 (0.47 – 3.14)	31	1.15 (0.68 – 1.96)	52	0.78 (0.54 – 1.12)	
WC (per 5 cm)	570	0.98 (0.94 – 1.02)	49	0.95 (0.81 – 1.10)	156	1.05 (0.97-1.14)	365	0.96 (0.91 – 1.01)	0.30
+ adjusted for BMI		1.18 (1.08 – 1.28)		0.77 (0.58 – 1.03)		1.21 (1.03 – 1.42)		1.23 (1.11 – 1.37)	
WHR (per 0.1 unit)	570	1.15 (0.99 – 1.32)	49	0.95 (0.58 – 1.56)	156	1.22 (0.94 – 1.60)	365	1.15 (0.97 – 1.37)	0.67
+ adjusted for BMI		1.43 (1.23 – 1.67)		0.89 (0.49 – 1.60)		1.32 (0.98 – 1.78)		1.58 (1.31 – 1.90)	
Women									
BMI									
<22.5 kg/m^2	58	1.58 (1.06 – 2.36)	11	1.34 (0.58 – 3.12)	9	0.82 (0.35 – 1.93)	38	2.29 (1.30 – 4.04)	0.20
22.5-24.9 kg/m^2	44	1.0 (ref)	11	1.0 (ref)	14	1.0 (ref)	19	1.0 (ref)	
25-29.9 kg/m^2	82	1.38 (0.95 – 2.01)	30	1.56 (0.78 – 3.15)	18	0.86 (0.42 – 1.77)	34	1.74 (0.99 – 3.08)	
≥30 kg/m^2	39	1.50 (0.96 – 2.35)	22	2.25 (1.06 -4.77)	7	0.83 (0.33 – 2.12)	10	1.28 (0.58 – 2.83)	
WC (per 5 cm)	223	1.08 (1.02 – 1.15)	74	1.12 (1.01 – 1.25)	48	1.01 (0.87 – 1.16)	101	1.09 (0.99 – 1.19)	0.39
+ adjusted for BMI		1.37 (1.22 – 1.54)		1.17 (0.96 – 1.43)		1.07 (0.82 – 1.39)		1.78 (1.50 – 2.11)	
WHR (per 0.1 unit)	223	1.64 (1.38 – 1.95)	74	1.26 (0.89 – 1.79)	48	1.02 (0.64 – 1.63)	101	2.09 (1.69 – 2.60)	0.003
+ adjusted for BMI		1.78 (1.49 – 2.12)		1.15 (0.79 – 1.70)		1.06 (0.64 – 1.77)		2.51 (2.00 – 3.15)	

[a] Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

[b] Cox regression models stratified by age, sex, centre, adjusted for education and alcohol intake