

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

Ward, HA, Wark, PA, Muller, DC, Steffen, A, Johansson, M, Norat, T, Gunter, MJ, Overvad, K, Dahm, CC, Halkjær, J, Tjønneland, A, Boutron-Ruault, M-C, Fagherazzi, G, Mesrine, S, Brennan, P, Freisling, H, Li, K, Kaaks, R, Trichopoulou, A, Lagiou, P, Panico, S, Grioni, S, Tumino, R, Vineis, P, Palli, D, Peeters, PHM, Bueno-de-Mesquita, HB, Weiderpass, E, Agudo, A, Ramon Quiros, J, Larrañaga, N, Ardanaz, E, Huerta, JM, Sánchez, M-J, Laurell, G, Johansson, I, Westin, U, Wallstrom, P, Bradbury, KE, Wareham, NJ, Khaw, K-T, Pearson, C, Boeing, H & Riboli, E

**Author post-print (accepted) deposited by Coventry University's Repository**

## **Original citation & hyperlink:**

Ward, HA, Wark, PA, Muller, DC, Steffen, A, Johansson, M, Norat, T, Gunter, MJ, Overvad, K, Dahm, CC, Halkjær, J, Tjønneland, A, Boutron-Ruault, M-C, Fagherazzi, G, Mesrine, S, Brennan, P, Freisling, H, Li, K, Kaaks, R, Trichopoulou, A, Lagiou, P, Panico, S, Grioni, S, Tumino, R, Vineis, P, Palli, D, Peeters, PHM, Bueno-de-Mesquita, HB, Weiderpass, E, Agudo, A, Ramon Quiros, J, Larrañaga, N, Ardanaz, E, Huerta, JM, Sánchez, M-J, Laurell, G, Johansson, I, Westin, U, Wallstrom, P, Bradbury, KE, Wareham, NJ, Khaw, K-T, Pearson, C, Boeing, H & Riboli, E 2017, 'Measured adiposity in relation to head and neck cancer risk in the European Prospective Investigation into Cancer and Nutrition' *Cancer Epidemiology Biomarkers and Prevention*, vol 26, no. 6, pp. 895-904

<https://dx.doi.org/10.1158/1055-9965.EPI-16-0886>

DOI 10.1158/1055-9965.EPI-16-0886

ISSN 1753-9153

ESSN 1753-9161

Publisher: American Association for Cancer Research

**Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.**

**This document is the author's post-print version, incorporating any revisions agreed during the peer-review process. Some differences between the published version and this version may remain and you are advised to consult the published version if you wish to cite from it.**

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

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

<sup>5</sup> Corresponding author. Email address: [heather.ward@imperial.ac.uk](mailto: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:**

<sup>1</sup> School of Public Health, Imperial College, St Mary's Campus, London W2 1PG, UK

<sup>2</sup> Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany

<sup>3</sup> International Agency for Research on Cancer (IARC-WHO), 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

<sup>4</sup> Section for Epidemiology, Department of Public Health, Aarhus University, DK-8000, Aarhus, Denmark

<sup>5</sup> Department of Cardiology, Aalborg University Hospital, Fredrik Bajers Vej 5 9100, Aalborg, Denmark

<sup>6</sup> Danish Cancer Society Research Centre, Diet, Genes and Environment, Strandboulevarden 49 DK-2100, Copenhagen, Denmark

<sup>7</sup> Université Paris-Saclay, Univ. Paris-Sud, UVSQ, Inserm, CESP, Generations and health, F-94805, Villejuif, France

<sup>8</sup> Gustave Roussy, F-94805, Villejuif, France

<sup>9</sup> Division of Cancer Epidemiology, German Cancer Research Centre, Im Neuenheimer Feld 280 69120, Heidelberg, Germany

<sup>10</sup> Hellenic Health Foundation, Kaisareias 13 & Alexandroupoleos GR-115 27 Athens, Greece

<sup>11</sup> Bureau of Epidemiologic Research, Academy of Athens, Leoforos Eleftheriou Venizelou 28, 106 79, Athens, Greece

<sup>12</sup> Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, 72-74 Vassilissis Sophias Avenue, 115 28, Athens, Greece

<sup>13</sup> Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, 02115 Boston, USA

<sup>14</sup> Department of Clinical Medicine and Surgery, Section of Endocrinology, Federico II University, Via Pansini, 5-80131, Naples, Italy

<sup>15</sup> Epidemiology and Prevention Unit; Fondazione IRCCS National Cancer Institute, via Venezian 1, 20133, Milano, Italy

<sup>16</sup> Cancer Registry and Histopathology Unit, Civic-M.P.Arezzo Hospital, Contrada Rito, 97100, ASP Ragusa, Italy

<sup>17</sup> HuGeF Foundation, Via Nizza 52, 10126 Torino, Italy

<sup>18</sup> Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute ISPO, Via delle Oblate 2, Florence, Italy

<sup>19</sup> Department of Epidemiology, Julius Centre for Health Sciences and Primary Care, University Medical Centre, Heidelberglaan 100, 3584 CX Utrecht, Netherlands

<sup>20</sup> National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9 3721 MA Bilthoven, Netherlands

- <sup>21</sup> Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Hansine Hansens veg 18, 9019, Tromsø, Norway
- <sup>22</sup> Cancer Registry of Norway – Institute of Population-Based Cancer Research, Ullernchausseen 64, 0379 Oslo, Norway
- <sup>23</sup> Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 5, 171 65 Solna, Stockholm, Sweden
- <sup>24</sup> Genetic Epidemiology Group, Folkhälsan Research Center, Haartmansgatan 8, 00290, Helsinki, Finland
- <sup>25</sup> Department of Biobank Research, Umeå University, Förvaltningshuset Universitetstorget 16, 901 87, Umeå, Sweden
- <sup>26</sup> Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology, Avda Gran Via 199-203 08908, Barcelona Spain
- <sup>27</sup> Public Health Directorate, Ciriaco Miguel Vigil St, 9 33006 Oviedo, Asturias, Spain
- <sup>28</sup> Public Health Division of Gipuzkoa-BIODONOSTIA, Basque Regional Health Department, Pº Dr. Beguiristain s/n, 20014 Donostia , San Sebastián Gipuzkoa Spain
- <sup>29</sup> Navarre Public Health Institute, Campus de Arrosadia, s/n, 31006 Pamplona, Spain
- <sup>30</sup> Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Ronda de Levante 11, 30008, Murcia, Spain
- <sup>31</sup> Andalusian School of Public Health, Research Institute Biosanitary Granada, 18080 Cuesta del Observatorio 4 Campus Universitario de Cartuja, Granada, Spain
- <sup>32</sup> CIBER Epidemiology and Public Health (CIBERESP), Av. Monforte de Lemos 3-5, 280289, Madrid, Spain
- <sup>33</sup> Department of Surgical Sciences, Uppsala University, University Hospital, SE-751 85 Uppsala, Sweden
- <sup>34</sup> Department of Odontology, Umeå University, SE 901 87, Umeå, Sweden
- <sup>35</sup> Ear Nose and Throat Department, Lund University, Dept of Otorhinolaryngology, University Hospital, SE-205 02, Malmö Sweden

<sup>36</sup> Nutrition Epidemiology Research Group, Department of Clinical Sciences, Lund University, Skåne University Hospital, SE-205 02 Malmö, Sweden

<sup>37</sup> Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Roosevelt Drive, OX3 7LF Oxford UK

<sup>38</sup> MRC Epidemiology Unit, University of Cambridge, School of Clinical Medicine, Institute of Metabolic Science, CB2 0SL Cambridge, UK

<sup>39</sup> University of Cambridge, Clinical Gerontology Unit, Addenbrooke's Hospital, Hills Road CB2 2QQ Cambridge, UK

<sup>40</sup> Cancer Research UK/Public Health England, London Road, London, SE1 6LH, UK

**Competing Interests:** The 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'Éducation 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<sup>2</sup>, normal weight (reference): 22.5-24.9 kg/m<sup>2</sup>, overweight 25-29.9 kg/m<sup>2</sup>, obese: ≥ 30 kg/m<sup>2</sup>], 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<sup>2</sup> 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









































- (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) Chioloro 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 <sup>a</sup>				Women <sup>a</sup>			
	BMI (kg/m <sup>2</sup> )				BMI (kg/m <sup>2</sup> )			
	<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

<sup>a</sup> 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		$P_{\text{interaction}}$ smoking status
	n cases	HR (95% CI) <sup>a</sup>	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	
<b>Men</b>									
<b>BMI</b>									
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	130	1.0 (ref)	13	1.0 (ref)	30	1.0 (ref)	87	1.0 (ref)	
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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
<b>Women</b>									
<b>BMI</b>									
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	55	1.0 (ref)	16	1.0 (ref)	15	1.0 (ref)	24	1.0 (ref)	
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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

---

<sup>a</sup> Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

<sup>b</sup> 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 <sup>a</sup>

	Oral cancer		Oropharyngeal cancer		Hypopharynx		Larynx		<i>P</i> heterogeneity HNC site
	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	
<b>Men</b>									
BMI									
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	21	1.0 (ref)	31	1.0 (ref)	17	1.0 (ref)	55	1.0 (ref)	
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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
<b>Women</b>									
BMI									
<22.5 kg/m <sup>2</sup>	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 <sup>c</sup>
22.5-24.9 kg/m <sup>2</sup>	26	1.0 (ref)	12	1.0 (ref)	1	1.0 (ref)	13	1.0 (ref)	
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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

<sup>a</sup> HNC site was defined as oro/hypopharynx not otherwise specified among 23 women and 28 men

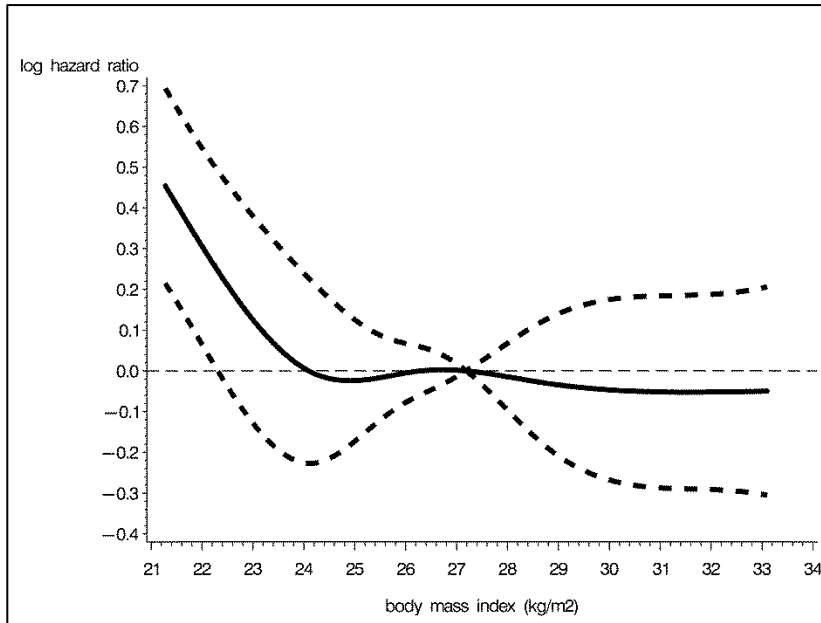
<sup>b</sup> Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

<sup>c</sup> 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/m<sup>2</sup>

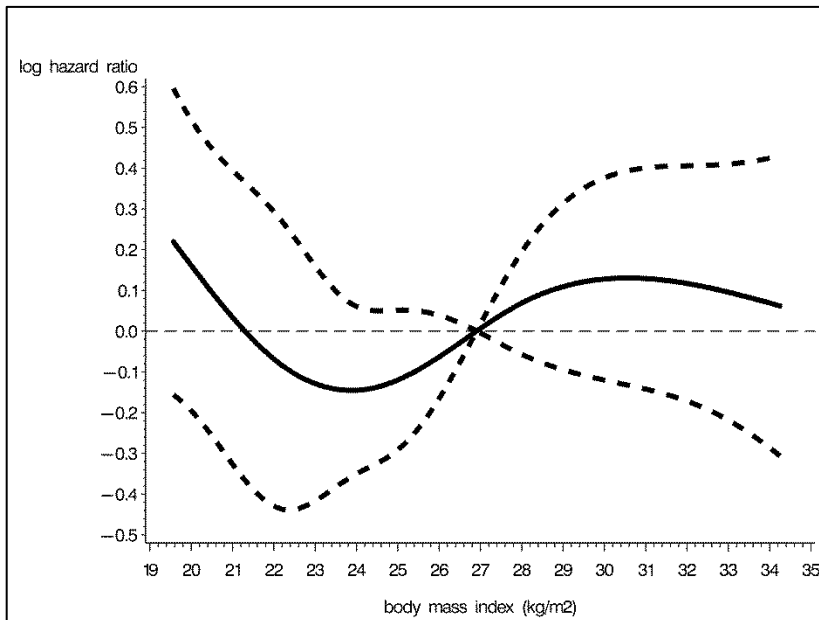
**Figure Legends:**

**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<sup>th</sup>, 25<sup>th</sup>, 75<sup>th</sup> and 95<sup>th</sup> percentiles of BMI, and models adjusted for education, alcohol intake, and smoking.



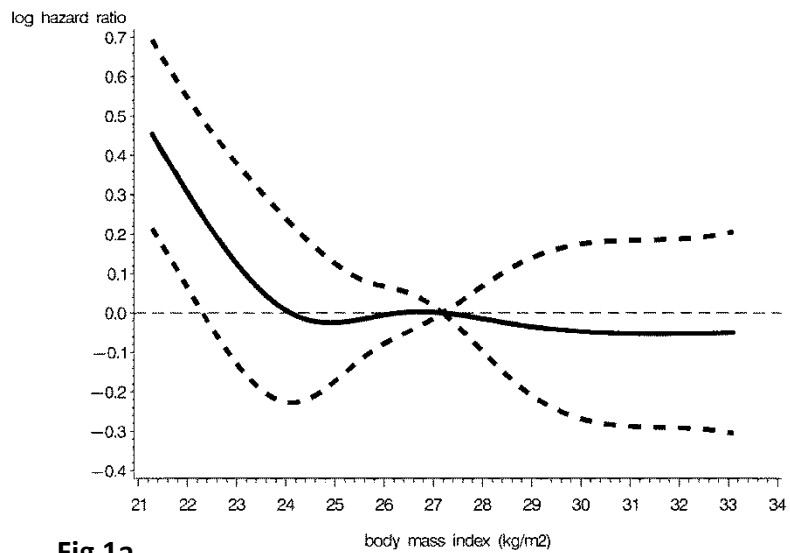


**Figure 1a**

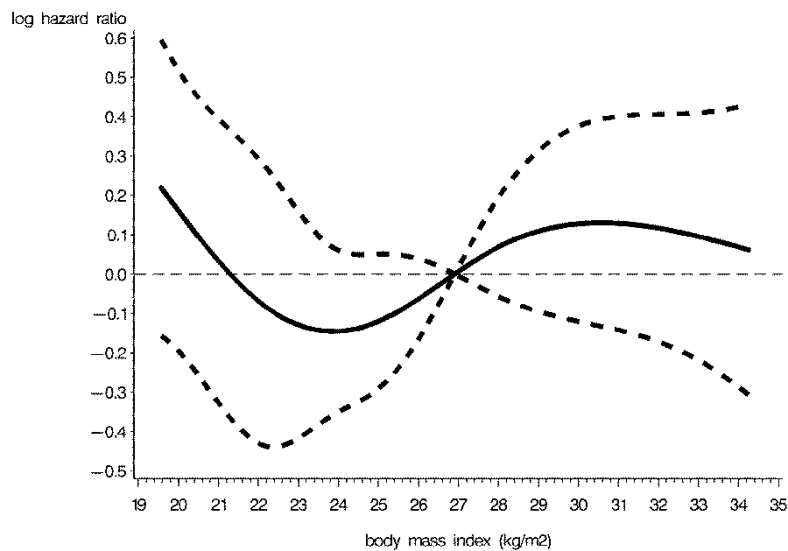


**Figure 1b**

**Figure 1.**

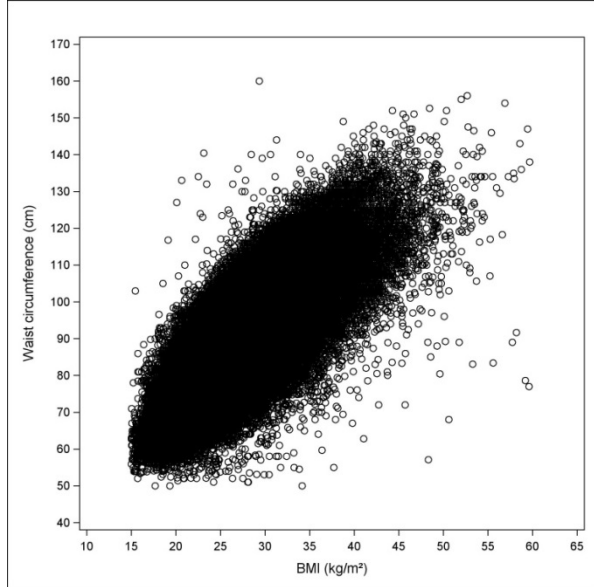


**Fig 1a.**

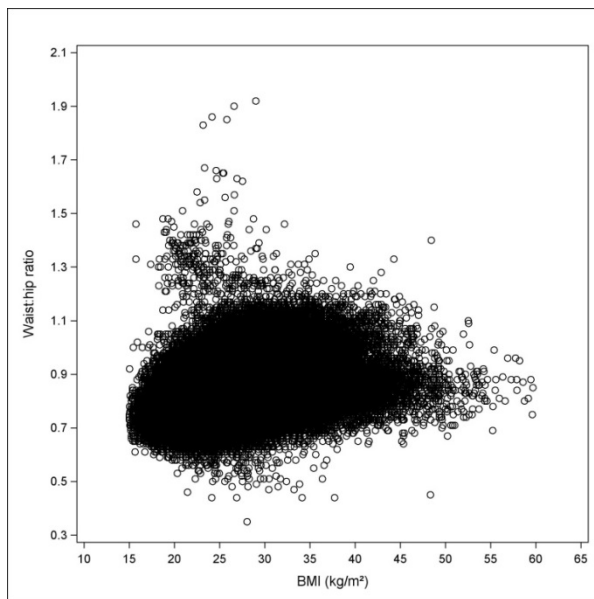


**Fig 1b.**

**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 5<sup>th</sup>, 25<sup>th</sup>, 75<sup>th</sup> and 95<sup>th</sup> 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/m<sup>2</sup>) and WC (Fig 1a) and between BMI (kg/m<sup>2</sup>) 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 <sup>a</sup>	Model 2 <sup>b</sup>	n cases	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
<b>Baseline BMI</b>						
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	69	1.0 (reference)	1.0 (reference)	37	1.0 (reference)	1.0 (reference)
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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)
<b>Smoking status</b>						
<b>Never</b>						
<b>Baseline BMI</b>						
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	9	1.0 (reference)	1.0 (reference)	13	1.0 (reference)	1.0 (reference)
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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)
<b>Former</b>						
<b>Baseline BMI</b>						
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	14	1.0 (reference)	1.0 (reference)	10	1.0 (reference)	1.0 (reference)
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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)
<b>Current</b>						
<b>Baseline BMI</b>						
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	46	1.0 (reference)	1.0 (reference)	14	1.0 (reference)	1.0 (reference)
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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

<sup>a</sup> Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

<sup>b</sup> 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 <sup>a</sup> questionnaire		Current smokers, baseline and second <sup>a</sup> questionnaire	
	n cases	HR (95% CI)	n cases	HR (95% CI)
<b>Men</b>				
Baseline BMI				
<22.5 kg/m <sup>2</sup>	5	1.69 (0.53 – 5.42)	30	1.51 (0.93 – 2.45)
22.5-24.9 kg/m <sup>2</sup>	7	1.0 (ref)	40	1.0 (ref)
25-29.9 kg/m <sup>2</sup>	20	1.74 (0.73 – 4.18)	80	0.89 (0.60 – 1.32)
≥30 kg/m <sup>2</sup>	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)
<b>Women</b>				
Baseline BMI				
<22.5 kg/m <sup>2</sup>	10	1.22 (0.50 – 2.98)	21	1.91 (0.90 – 4.09)
22.5-24.9 kg/m <sup>2</sup>	10	1.0 (ref)	11	1.0 (ref)
25-29.9 kg/m <sup>2</sup>	21	1.32 (0.61 – 2.86)	16	1.38 (0.62 – 3.05)
≥30 kg/m <sup>2</sup>	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)

<sup>a</sup> Second questionnaire completed on average 5 years after baseline

<sup>b</sup> 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		<i>p</i> for interaction by smoking status
	n cases	HR (95% CI) <sup>a</sup>	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	n cases	HR (95% CI) <sup>b</sup>	
<b>Men</b>									
<b>BMI</b>									
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	125	1.0 (ref)	11	1.0 (ref)	28	1.0 (ref)	86	1.0 (ref)	
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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) + adjusted for BMI	570	0.98 (0.94 – 1.02) 1.18 (1.08 – 1.28)	49	0.95 (0.81 – 1.10) 0.77 (0.58 – 1.03)	156	1.05 (0.97-1.14) 1.21 (1.03 – 1.42)	365	0.96 (0.91 – 1.01) 1.23 (1.11 – 1.37)	0.30
WHR (per 0.1 unit) + adjusted for BMI	570	1.15 (0.99 – 1.32) 1.43 (1.23 – 1.67)	49	0.95 (0.58 – 1.56) 0.89 (0.49 – 1.60)	156	1.22 (0.94 – 1.60) 1.32 (0.98 – 1.78)	365	1.15 (0.97 – 1.37) 1.58 (1.31 – 1.90)	0.67
<b>Women</b>									
<b>BMI</b>									
<22.5 kg/m <sup>2</sup>	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 <sup>2</sup>	44	1.0 (ref)	11	1.0 (ref)	14	1.0 (ref)	19	1.0 (ref)	
25-29.9 kg/m <sup>2</sup>	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 <sup>2</sup>	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) + adjusted for BMI	223	1.08 (1.02 – 1.15) 1.37 (1.22 – 1.54)	74	1.12 (1.01 – 1.25) 1.17 (0.96 – 1.43)	48	1.01 (0.87 – 1.16) 1.07 (0.82 – 1.39)	101	1.09 (0.99 – 1.19) 1.78 (1.50 – 2.11)	0.39
WHR (per 0.1 unit) + adjusted for BMI	223	1.64 (1.38 – 1.95) 1.78 (1.49 – 2.12)	74	1.26 (0.89 – 1.79) 1.15 (0.79 – 1.70)	48	1.02 (0.64 – 1.63) 1.06 (0.64 – 1.77)	101	2.09 (1.69 – 2.60) 2.51 (2.00 – 3.15)	0.003

<sup>a</sup> Cox regression models stratified by age, sex, centre and smoking status, adjusted for education and alcohol intake

<sup>b</sup> Cox regression models stratified by age, sex, centre, adjusted for education and alcohol intake