Title
General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition.

Journal
International journal of cancer, 137(3)

ISSN
0020-7136

Authors
Steffen, Annika
Huerta, José-Maria
Weiderpass, Elisabete
et al.

Publication Date
2015-08-01

DOI
10.1002/ijc.29432

IJC
International Journal of Cancer

General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition

Annika Steffen[1], José-Maria Huerta[2,3], Elisabete Weiderpass[4,5,6,7], H.B(as) Bueno-de-Mesquita[8,9,10,11], Anne M. May[12], Peter D. Siersema[9], Rudolf Kaaks[13], Jasmine Neamat-Allah[13], Valeria Pala[14], Salvatore Panico[15], Calogero Saieva[16], Rosario Tumino[17], Alessio Naccarati[18], Miren Dorronsoro[19], Emilio Sánchez-Cantalejo[3,20], Eva Ardanaz[3,21], J. Ramón Quirós[22], Bodil Ohlsson[23], Mattias Johansson[24,25], Bengt Wallner[26], Kim Overvad[27], Jytte Halkjær[28], Anne Tjønneland[28], Guy Fagherazzi[29,30,31], Antoine Racine[29,30,31], Françoise Clavel-Chapelon[29,30,31], Tim J. Key[32], Kay-Tee Khaw[33], Nick Wareham[34], Pagona Lagiou[35,36,37], Christina Bamia[35], Antonia Trichopoulou[38,39], Pietro Ferrari[25], Heinz Freisling[25], Yunxia Lu[40], Elio Riboli[40], Amanda J. Cross[40], Carlos A. Gonzalez[41] and Heiner Boeing[1]

[1] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany
[2] Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain
[3] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[4] Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway
[5] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[6] Cancer Registry of Norway, Oslo, Norway
[7] Samfundet Folkhalsan, Helsinki, Finland
[8] National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
[9] Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands
[10] Department of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, London, United Kingdom
[11] Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[12] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
[13] Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany
[14] Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[15] Dipartmento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy
[16] Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute—ISPO, Florence, Italy
[17] Cancer Registry and Histopathology Unit, "Civic-M.P. Arezzo" Hospital, ASP Ragusa, Ragusa, Italy
[18] Human Genetics Foundation (HuGeF), Torino, Italy
[19] Public Health Direction and Biodonostia—Ciberesp, Basque Regional Health Department, Vitoria, Spain
[20] Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria de Granada, Granada, Spain
[21] Navarre Public Health Institute, Pamplona, Spain
[22] Public Health Directorate, Asturias, Spain
[23] Division of Internal Medicine, Department of Clinical Sciences, Skåne University Hospital, Malmö, Lund University, Lund, Sweden

Epidemiology

Key words: general obesity, abdominal obesity, body mass index, waist circumference, gastric cancer, esophageal cancer

Abbreviations: BMI: body mass index; EAC: esophageal adenocarcinoma; EPIC: European Prospective Investigation into Cancer and Nutrition; GCC: gastric cardia carcinoma; GNCC: gastric non-cardia carcinoma; HC: hip circumference; HR: hazard ratio; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio

Conflict of interest: none

Grant sponsors: European Commission (DG-SANCO), International Agency for Research on Cancer, Deutsche Krebshilfe, German Cancer Research Center, German Federal Ministry of Education and Research, Danish Cancer Society; **Grant sponsor:** Health Research Fund (FIS) of the Spanish Ministry of Health; **Grant number:** Network RCESP C03/09; **Grant sponsor:** Spanish Regional Governments of Andalucia, Asturias, Basque Country and Navarra; **Grant sponsor:** Spanish Regional Government of Murcia; **Grant number:** 6236; **Grant sponsors:** ISCIII, Red de Centros RETIC (RD06/0020); **Grant number:** C03/09; **Grant sponsors:** Cancer Research UK, Medical Research Council, UK, Italian Association for Research on Cancer (AIRC), Compagnia di San Paolo, Dutch Ministry of Public Health, Welfare and Sports, National Cancer Registry and the Regional Cancer Registries Amsterdam, East and Maastricht of the Netherlands, Hellenic Health Foundation, World Cancer Research Fund (WCRF), Swedish Cancer Society, Swedish Scientific Council, Regional Government of Skåne and Västerbotten, Sweden

DOI: 10.1002/ijc.29432

History: Received 20 Oct 2014; Accepted 27 Nov 2014; Online 17 Jan 2015

Correspondence to: Annika Steffen, German Institute of Human Nutrition (DIfE) Potsdam-Rehbruecke, Department of Epidemiology, Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany, Tel.: +[49-(0)33200-88-2717], Fax:+[49-(0)33200-88-2721], E-mail: annika.steffen@dife.de

[24] Department for Biobank Research, Umeå University, Umeå, Sweden
[25] International Agency for Research on Cancer (IARC-WHO), Lyon, France
[26] Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden
[27] Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark
[28] Danish Cancer Society Research Center, Copenhagen, Denmark
[29] Inserm, Centre for research in Epidemiology and Population Health (CESP), Nutrition, Hormones and Women's Health team, Villejuif, France
[30] Univ Paris Sud, Villejuif, France
[31] IGR, Villejuif, France
[32] Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom
[33] University of Cambridge, Cambridge, United Kingdom
[34] MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom
[35] Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece
[36] Department of Epidemiology, Harvard School of Public Health, Boston, MA
[37] Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece
[38] Hellenic Health Foundation, Athens, Greece
[39] Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece
[40] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom
[41] Unit of Nutrition, Environment and Cancer, Programme of Epidemiological Research, Catalan Institute of Oncology, Barcelona (ICO-IDIBELL), Spain

General obesity, as reflected by BMI, is an established risk factor for esophageal adenocarcinoma (EAC), a suspected risk factor for gastric cardia adenocarcinoma (GCC) and appears unrelated to gastric non-cardia adenocarcinoma (GNCC). How abdominal obesity, as commonly measured by waist circumference (WC), relates to these cancers remains largely unexplored. Using measured anthropometric data from 391,456 individuals from the European Prospective Investigation into Cancer and Nutrition (EPIC) study and 11 years of follow-up, we comprehensively assessed the association of anthropometric measures with risk of EAC, GCC and GNCC using multivariable proportional hazards regression. One hundred twenty-four incident EAC, 193 GCC and 224 GNCC were accrued. After mutual adjustment, BMI was unrelated to EAC, while WC showed a strong positive association (highest *vs*. lowest quintile HR = 1.19; 95% CI, 0.63–2.22 and HR = 3.76; 1.72–8.22, respectively). Hip circumference (HC) was inversely related to EAC after controlling for WC, while WC remained positively associated (HR = 0.35; 0.18–0.68, and HR=4.10; 1.94-8.63, respectively). BMI was not associated with GCC or GNCC. WC was related to higher risks of GCC after adjustment for BMI and more strongly after adjustment for HC (highest *vs*. lowest quintile HR = 1.91; 1.09–3.37, and HR = 2.23; 1.28–3.90, respectively). Our study demonstrates that abdominal, rather than general, obesity is an indisputable risk factor for EAC and also provides evidence for a protective effect of gluteofemoral (subcutaneous) adipose tissue in EAC. Our study further shows that general obesity is not a risk factor for GCC and GNCC, while the role of abdominal obesity in GCC needs further investigation.

What's new?

While mainly general obesity, as measured by body mass index, has been investigated in relation to gastric and esophageal cancer, the effect of a large waist on these cancer sites is unknown. In this article, the authors report results of extensive analysis of measured anthropometry, including measures of general (BMI) and abdominal obesity (waist circumference), collected by the European Prospective Investigation into Cancer and Nutrition (EPIC). They show that general obesity is not a risk factor for esophageal and gastric cancer, while waist circumference strongly increases risk of esophageal cancer and may potentially be related to gastric cardia cancer.

Epidemiology

Over recent decades, the continuous rise in incidence of esophageal adenocarcinoma (EAC) has been well documented.[1] Though less marked, the incidence of gastric cardia carcinoma (GCC) has also been on the rise in several Western countries. In contrast, the incidence of gastric non-cardia cancers (GNCC) has continuously decreased over the past 50 years,[2] most likely due to a marked decline in *Helicobacter pylori* infection, the single most common cause of GNCC accounting for 75% of cases.[3]

The rise in EAC and GCC incidence has been paralleled by the worldwide increase in obesity prevalence and excess body weight has been suggested to at least partially explain the rise in both cancer types. While evidence on the association of general obesity, as measured by the body-mass-index (BMI), with EAC has been judged convincing by the World Cancer Research Fund,[4] evidence for an association with GCC has remained less conclusive. Recently, a meta-analysis based on seven prospective studies and 800 cases concluded

BMI to be a risk factor for GCC.[5] However, half of the included studies (470 GCC cases) relied on self-reported anthropometric data which, in case of BMI, might result in an overestimation of relative risks.[6] Hence, when meta-analysis was stratified by ascertainment of BMI, Chen *et al.* found substantially weaker associations among studies based on measured weight and height compared to studies based on self-reported anthropometrics.[5]

During recent years, evidence has accumulated that body fat distribution, *i.e.* abdominal obesity, as commonly reflected by waist circumference (WC), may better predict risk of several chronic diseases and mortality than general obesity (BMI).[7–11] On that note, we previously found evidence that abdominal obesity may exert an effect beyond the effect of general obesity in relation to EAC, though statistical power was limited.[12] How abdominal obesity relates to gastric cancer remains largely unexplored. So far, two prospective studies have reported associations between measures of abdominal obesity and GCC, with conflicting results.[13,14] Hardly, any data exists in relation to GNCC.

Based on measured anthropometric data from 391,456 individuals participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, we aimed to comprehensively assess the association of anthropometric measures, including body height, BMI, waist and hip circumference, waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), with anatomic subtypes of gastric cancer and present an update of our previous study on EAC,[12] now based on a larger number of cases.

Material and Methods

Study population

The EPIC study is a multicenter prospective study designed primarily to investigate the relation between diet and the incidence of cancer and other chronic diseases.[15,16] Between 1992 and 2000, sub-cohorts were recruited at 23 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom (UK). The 521,448 eligible men and women were mostly aged 25–70 years and recruited from the general population residing in a given geographical area. Exceptions were the French cohorts (based on female members of the health insurance for school employees), the Oxford cohort in the UK (based on vegetarian volunteers and healthy eaters), parts of the Italian and Spanish cohorts (based on blood donors) and the cohorts in Utrecht (The Netherlands) and Florence (Italy) which were based on women attending breast cancer screening. Eligible subjects were invited to participate and those who gave informed consent completed questionnaires on diet, lifestyle and medical history. Participants were then invited to a center to have anthropometric measurements taken by trained staff.

We excluded 28,268 individuals with prevalent cancer (other than non-melanoma skin cancer) or because they were lost to follow-up ($n = 15$). Further exclusions refer to individuals for whom data on measured weight and height were missing ($n = 92{,}440$), among them the cohort of Norway ($n = 35{,}889$), 48,616 participants from the French cohorts and 7,935 from the other cohorts. We additionally excluded 1,495 participants with missing questionnaire data and — to reduce the effect of implausible extreme values on the analysis — 7,772 individuals who were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement that was calculated from height, weight, gender and age. For analyses on EAC, participants from Greece and the remaining participants from France were additionally excluded because they did not contribute any cases, partly due to incomplete case identification routines for this cancer site.

After exclusions, 391,456 (141,122 men and 250,334 women) with complete information on height and weight remained for analyses (75% of the original eligible cohort), while analyses involving WC and HC were restricted to 360,755 individuals. For EAC, analyses on weight and height comprised 345,738 men and women and analyses on WC and HC 315,088 persons.

Assessment of anthropometric data, diet and lifestyle factors

Weight and height were measured according to standardized protocols by trained personnel to the nearest 0.1 kg and 0.1 or 0.5 cm, respectively, with subjects wearing no shoes, as described in detail previously.[17] WC was measured either at the narrowest torso circumference (most centers) or midway between the lower ribs and iliac crest. Hip circumference was measured horizontally at the widest circumference or over the buttocks. In Umeå (Sweden), anthropometric data collection was restricted to measurement of weight and height. Body weight, WC and HC were adjusted for heterogeneity due to protocol differences in clothing worn during measurement.[17] For the "health conscious group" based in Oxford (UK), linear regression models were used to predict sex- and age-specific values from participants with both measured and self-reported body measures as previously described.[18] BMI was calculated as weight in kg divided by height in meters squared (kg/m^2), WHR was calculated as WC (cm) divided by HC (cm) and WhtR was calculated as WC (cm) divided by height (m).

Lifestyle questionnaires included questions on smoking habits at baseline and history of tobacco consumption, alcohol use, education and occupational and recreational physical activity. The information on occupational activity (coded as sedentary, standing, manual, heavy manual, unemployed or missing) and the sum of the recreational activities cycling and sports (hr/week, coded in four categories: none, $\leq$3.5, 3.5–7.0 and $>$7.0) were used to create a variable for total physical activity by cross-classifying participants into five categories (inactive, moderately inactive, moderately active, active and missing).[19] Usual diet was assessed by validated country-specific food frequency questionnaires designed to capture local dietary habits and to ensure high compliance.[15]

We lacked information on *H. pylori* infection which may be a confounder for the association with EAC as it may be related to reduced obesity[20] and to lower risk of EAC.[21] History of reflux symptoms, an important risk factor for EAC, was also not collected in our study. However, as reflux symptoms could be on the causal pathway between obesity and EAC,[22] it is unclear whether adjustment is desirable. Finally, we lacked information on nonsteroidal anti-inflammatory drug (NSAID) use, a protective factor for gastric cancer.[23,24] However, as NSAID use does not appear to strongly correlate with obesity,[13,25] its role as important confounder remains unclear.

Follow-up and ascertainment of endpoints

Identification of cancer cases was based on population cancer registries (Denmark, Italy, Netherlands, Spain, Sweden and United Kingdom) or a combination of methods including regional and local cancer registries together with an active follow-up through participants and their next-of-kin (Germany and Naples). Mortality data were also collected from either the cancer registry or mortality registries. Participants were followed up from study entry until cancer incidence, death or end of follow-up, whichever came first. Censoring dates for complete follow-up from cancer registries were between December 2004 and December 2008. For centers with active follow-up, the end of follow-up was considered to be the date of diagnosis, date of the last known contact or date of death, whichever came first.

Mortality data were coded following the rules of the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10) and cancer incidence data following the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). Morphology information was used to classify the malignant tumors according to histological type. We included first incident primary adenocarcinomas of the esophagus coded as C15 ($n = 133$ before exclusions) and stomach coded as C16 (C16.0 for cardia and C16.1–16.6 for non-cardia, $n = 452$ before exclusions); C16.8 (overlapping tumors) and C16.9 (not otherwise specified) were not considered. Validation and confirmation of the diagnosis, classification of tumor site and of tumor morphology were performed, for about 50% of the cases, by a panel of pathologists.[26] Gastro-esophageal junction (GEJ) tumors were combined with proximal gastric tumors as GCC.

Statistical analysis

Associations of anthropometric measures with EAC and gastric cancer were analyzed using Cox proportional hazards regression. Age at recruitment was taken as the underlying time variable with entry and exit time defined as the participant's age at recruitment and age at diagnosis or censoring, respectively. All models were stratified by study center and age to control for differences in questionnaire design, follow-up procedures and other non-measured center effects, and to be more robust against violation of the proportionality assumption. Departure from the proportional hazards assumption was evaluated for all endpoints by including an interaction term of time and the respective anthropometric variable in the model. No violations were detected.

Because there was no interaction for sex with any anthropometric variable and cancer outcome, we present results for men and women combined. Since restricted cubic spline models provided evidence for non-linear associations between some anthropometric measures and gastric cancer subtypes, participants were categorized into quintiles. We used sex-specific quintiles based on the anthropometric variables of the entire male or female cohorts, respectively, to account for different body fat distributions of men and women. Tests for trend across quintiles of anthropometric variables were performed by assigning each participant the median category value and modeling this value as a continuous variable. We also performed additional analyses by grouping individuals into predefined well-established categories of BMI (18.5–<25 for normalweight, 25–<30 for overweight and $\geq$30 kg/m^2 for obese).[27]

Relative risks were adjusted for sex, education (no school or primary school degree, technical/professional school degree, secondary school degree, university degree, not specified), smoking habits (lifelong non-smoker, former smoking ceased $\geq$10 years, former smoking ceased <10 years, current smoking with <15 cig/day, current smoking with 15–24 cig/day, current smoking with $\geq$25 cig/day and current smoking with unknown quantity or smoking other than cigarettes, missing), alcohol consumption at recruitment (yes/no) and amount of alcohol (g/day), physical activity (inactive, moderately inactive, moderately active, active and missing) and intake of red and processed meat, vegetables, citrus and non-citrus fruits (g/day). Models for weight, BMI, WC, HC, WHR and WHtR were adjusted for height and models for height were adjusted for BMI.[28]

Although WHR is widely used as a measure of body fat distribution, its interpretation in relation to disease risk is complicated by its nature as a ratio of two complex variables.[28] Increased WHR can reflect both increased visceral fat mass through higher WC and/or reduced gluteofemoral muscle mass through lower HC and does not allow to evaluate the unique properties of WC and HC independently of each other on health risk.[29] WC reflects both visceral and subcutaneous adipose tissue, while HC provides a more specific measure of subcutaneous adipose tissue (albeit at a different location). This was recently underlined in a subsample of the German EPIC cohorts using magnetic resonance imaging.[30] Therefore, mutual adjustment of WC and HC results in a more precise effect measure of visceral and gluteofemoral (subcutaneous) adipose tissue, respectively.[28,31] For the sake of consistency with previous publications, we do present results for WHR, but focus on analyses that mutually adjusted WC and HC. To circumvent problems due to collinearity, we used the residual method for adjustment.

Likewise, we mutually adjusted WC and BMI to estimate whether abdominal obesity is associated with cancer risk beyond the association with general obesity.

In sensitivity analyses, we examined associations across strata of smoking status and after exclusion of cases occurring during the first two years of follow-up to exclude reverse causation.

All p-values presented are two-tailed and $p < 0.05$ was considered statistically significant. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

During an average (SD) of 11.2 (2.9) years, 124 EAC cases (100 men, 24 women) and 641 GC cases (391 men, 250 women) were diagnosed among 391,456 participants (4,397,365 person-years). Of these cases, 193 were GCC (144 men, 49 women), 224 GNCC (120 men and 104 women) and 224 of overlapping, not specified or unknown anatomic location (Table 1).

Cohort characteristics across sex-specific quintiles of BMI are presented in Table 2. Men and women with higher BMI were older, more likely to be physically inactive, less likely to have a university degree and reported higher intake of red and processed meat. Correlations of BMI with WC, HC, WHR and WHtR were 0.78, 0.83, 0.43 and 0.86, respectively. Correlation of WC with HC was 0.67.

In relation to EAC, all obesity measures were consistently related to higher risks (Table 3). The hazard ratios for highest *vs.* lowest quintile were HR = 2.15, 95% CI, 1.14–4.05; HR = 5.08, 95% CI, 2.21–11.7; HR = 3.94, 95% CI, 1.87–8.31 and HR = 5.21, 95% CI, 2.10–13.0, for BMI, WC, WHR and WHtR respectively. Across established categories of BMI, the HRs for overweight and obesity compared to normalweight were HR = 1.32, 95% CI, 0.87–1.99 and HR = 1.66, 95% CI, 0.97–2.87, respectively (data not shown). After mutual adjustment of BMI and measures of abdominal obesity (Table 4), BMI was no longer related to EAC, while the association with WC remained strongly positive and clearly significant (for highest *vs.* lowest quintile HR = 1.19, 95% CI, 0.63–2.22; HR = 3.76, 95% CI, 1.72–8.22 for BMI and WC, respectively). Hip circumference showed a strong inverse association after adjustment for WC (HR = 0.35, 95% CI, 0.18–0.68, for highest *vs.* lowest quintile), while WC remained strongly positively associated (HR = 4.10, 95% CI, 1.94–8.63).

For GCC, we did not observe an association with BMI across quintiles (HR = 1.17, 95% CI, 0.71–1.92, for highest *vs.* lowest quintile, Table 3) nor for established BMI categories (HR = 1.18, 95% CI, 0.86–1.63 and HR = 1.10, 95% CI, 0.69–1.74, for overweight and obesity, respectively). However, we found a positive association between measures of abdominal obesity and GCC (HR = 1.59, 95% CI, 0.93–2.73; HR = 2.18, 95% CI, 1.24–3.83 and HR = 1.78, 95% CI, 1.00–3.18, for WC, WHR and WHtR for highest *vs.* lowest quintile, with p for trends of 0.06, 0.002 and 0.03,

Table 1. Distribution of incident cancer cases and means of anthropometric measures across centers of the EPIC study (n = 391,456)

				Gastric cancer				Mean (SD) of anthropometric measures					
					Anatomic site		Histology	BMI (kg/m^2)		WC (cm)		WHR	
Country	Cohort size (n)	Person-years	EAC[1]	Total[2]	Cardia	Non-cardia	Diffuse[2]	Intestinal[2]	Men	Women	Men	Women	Men	Women
France	19,810	211,532	NA	7	4	1	3	2	NA	23.4 (3.7)	NA	76.6 (9.5)	NA	0.78 (0.07)
Italy	44,195	496,096	2	84	15	44	39	35	26.4 (3.4)	25.7 (4.3)	92.6 (9.3)	80.1 (10.7)	0.93 (0.06)	0.80 (0.07)
Spain	39,612	477,769	4	77	7	40	26	32	28.4 (3.4)	28.1 (4.7)	99.4 (9.0)	87.3 (11.2)	0.95 (0.06)	0.82 (0.06)
United Kingdom	73,816	820,195	45	94	47	18	13	24	25.4 (3.5)	24.2 (4.2)	91.5 (9.4)	75.0 (9.6)	0.92 (0.06)	0.76 (0.06)
The Netherlands	36,487	431,050	9	43	15	17	14	8	25.5 (3.5)	25.2 (4.1)	90.5 (10.8)	80.7 (10.7)	0.91 (0.07)	0.79 (0.07)
Greece	25,908	246,543	NA	34	4	12	14	13	27.8 (3.8)	28.6 (5.2)	98.1 (10.5)	87.6 (12.7)	0.95 (0.07)	0.82 (0.08)
Germany	48,139	476,345	6	89	19	44	43	29	27.0 (3.6)	25.6 (4.6)	95.4 (10.1)	80.8 (11.6)	0.94 (0.06)	0.80 (0.07)
Sweden	48,510	636,765	25	108	34	29	27	27	25.6 (3.5)	24.8 (4.3)	93.7 (10.0)	77.8 (10.4)	0.94 (0.06)	0.79 (0.05)
Denmark	54,979	601,070	33	105	48	19	19	25	26.6 (3.6)	25.6 (4.4)	96.0 (9.9)	82.0 (11.2)	0.96 (0.06)	0.81 (0.07)
Total	391,456	4,397,365	124	641	193	224	198	195	26.5 (3.7)	25.4 (4.6)	94.8 (10.2)	80.2 (11.5)	0.94 (0.06)	0.07)

[1]EAC, Esophageal adenocarcinoma. France and Greece were excluded from the analysis on EAC due to incomplete case identification routines for this cancer site.
[2]There were 224 cases of overlapping, not otherwise specified or unknown site and 248 for histology was undetermined or mixed.

Table 2. Baseline characteristics across quintiles of BMI among men and women in the EPIC study ($n = 391,456$)

	BMI quintiles (median) among men (n=141,122)					BMI quintiles (median) among women (n=250,334)				
Characteristic	**Q1 (22.2)**	**Q2 (24.5)**	**Q3 (26.2)**	**Q4 (28.0)**	**Q5 (31.1)**	**Q1 (20.5)**	**Q2 (22.7)**	**Q3 (24.6)**	**Q4 (27.1)**	**Q5 (31.6)**
N	23,646	28,338	24,840	21,276	27,483	47783	40092	56048	43341	47909
Age (years)	49.4 (11.9)	51.9 (10.2)	52.7 (9.6)	53.4 (9.2)	53.7 (8.9)	46.5 (10.9)	49.6 (10.3)	51.7 (10.1)	53.2 (9.8)	55.2 (9.3)
Smoking (%)										
Lifelong non-smoker	36	32	30	27	26	47	47	48	53	61
Former, $\geq$10 years ago	9	11	13	15	17	8	9	9	8	8
Former, $<$10 years ago	16	22	23	24	23	13	14	14	13	11
Current, <15 cig/day	9	8	7	7	7	9	9	8	7	5
15–24 cig/day	10	8	8	8	8	6	6	6	6	4
$\geq$ 25 cig/day	4	4	4	5	6	1	1	1	1	1
Current, other than cigarette	15	15	13	13	12	15	13	13	11	9
Unknown	1	1	1	1	1	1	1	1	1	1
Education (%)										
None or primary school	22	28	32	37	47	14	21	30	41	55
Techn. or prof. school	24	25	25	24	23	23	26	25	24	20
Secondary school	17	14	13	11	10	24	21	18	15	11
University degree	34	31	27	22	18	35	28	21	15	10
Not specified	3	3	3	2	2	4	5	5	4	4
Physical activity (%)										
Inactive	16	16	18	20	24	17	18	22	28	39
Moderately inactive	30	31	31	31	30	36	36	36	34	31
Moderately active	25	25	24	24	23	27	25	23	20	17
Active	26	26	25	23	21	20	20	18	15	12
Unknown	3	2	2	2	2	2	2	2	1	1

Table 2. Baseline characteristics across quintiles of BMI among men and women in the EPIC study ($n = 391,456$) (Continued)

	BMI quintiles (median) among men (n=141,122)					BMI quintiles (median) among women (n=250,334)				
Characteristic	Q1 (22.2)	Q2 (24.5)	Q3 (26.2)	Q4 (28.0)	Q5 (31.1)	Q1 (20.5)	Q2 (22.7)	Q3 (24.6)	Q4 (27.1)	Q5 (31.6)
Alcohl consumer (%)	94	94	94	93	92	90	89	86	81	72
Baseline alcohol intake (g/day)[1]	11.5 (4.1,25.1)	13.2 (5.3,28.7)	14.4 (5.8,30.9)	15.5 (6.2,33.4)	16.3 (6.0,36.7)	6.0 (1.7,13.0)	6.3 (1.9,13.4)	5.9 (1.7,13.1)	5.3 (1.5,12.4)	3.6 (1.2,10.4)
Red meat (g/1000kcal)[1]	15.9 (6.4,29.0)	19.4 (9.2,32.0)	20.7(10.7,33.0)	21.9 (11.9,34.2)	23.6 (13.3, 35.6)	12.5 (3.1,24.7)	15.9 (6.5,27.8)	17.9 (8.6,29.6)	19.5 (10.1,30.8)	20.2 (10.8,31.4)
Processed meat (g/1000 kcal)[1]	12.6 (5.0, 21.6)	13.8 (6.7,22.8)	14.4 (7.2,23.9)	15.0 (7.4,25.1)	15.5 (7.1,26.5)	8.4 (2.4,16.3)	9.6 (3.8,17.6)	10.5 (4.7,18.6)	10.8 (4.9,19.3)	10.9 (3.9,20.4)
Vegetable (g/1000kcal)[1]	59.3 (36.4, 98.4)	62.0 (38.8,99.8)	63.5 (39.7,103.4)	66.1 (41.2,110.8)	69.7 (42.3,124.1)	94.8 (60.9,144.9)	94.3 (61.4,144.0)	93.9 (61.9,143.8)	96.6 (63.4,150.1)	103.7 (66.3,169.0)
Citrus fruits (g/1000kcal)[1]	7.5 (2.9,20.6)	8.7 (3.3, 23.8)	9.3 (3.3,25.4)	10.1 (3.3-28.2)	11.4 (3.4,32.1)	16.1 (5.5,33.9)	18.5 (6.4,38.1)	20.1 (6.9,41.0)	21.9 (7.4,45.0)	24.9 (8.3,50.2)
Non-citrus fruits (g/1000kcal)[1]	41.7 (19.8,75.7)	46.7 (22.8,83.2)	47.8 (23.4,87.0)	51.1 (24.7,92.9)	53.8 (25.5,97.6)	71.3 (37.7,117.0)	77.4 (43.1,123.3)	80.5 (45.1,128.3)	85.8 (48.1,135.7)	90.8 (50.2,141.9)

Presented are means (SD) or percentages.
[1]Median and interquartile range. For alcohol, among consumers only.

respectively). After additional adjustment for BMI (Table 4), the positive association with WC became more pronounced (HR = 1.91, 95% CI, 1.09–3.37, for highest *vs.* lowest quintile). Interestingly, the association with WC became even stronger after accounting for HC, while HC adjusted for WC tended toward an inverse relation (HR = 2.23, 95% CI, 1.28–3.90 and HR = 0.68, 95% CI, 0.42–1.13, for highest *vs.* lowest quintile, with p for trends 0.002 and 0.07, respectively).

BMI was unrelated to GNCC across quintiles (Table 3) and predefined BMI categories (HR = 0.99, 95% CI, 0.72–1.36 and HR = 1.19, 95% CI, 0.80–1.75, for overweight and obesity, respectively). Also, no consistent associations were observed for measures of abdominal obesity (Table 3). After adjusting for HC, estimates for WC became statistically significant (HR = 2.41, 95% CI, 1.32–4.40 for highest *vs.* lowest quintile of WC, with p for trend 0.01, Table 4).

When we cross-classified gastric cancers according to anatomy and histology, we observed no marked differences in comparison to the overall results (data not shown), however case numbers were too low to robustly evaluate associations for histologic type by anatomic subtype. Patterns of associations were largely similar across strata of smoking status (all p for interaction >0.05, data not shown), it may be noted though that case numbers across strata were relatively low, particularly among non-smokers. Results did not materially alter after exclusion of cases occurring during the first 2 years of follow-up (data not shown).

Discussion

Based on measured anthropometric data, this relatively large European cohort study consistently demonstrates abdominal obesity, rather than general obesity, as a robust and indisputable risk factor for the development of EAC. Interestingly, our study provides new evidence on the potentially protective role of higher gluteofemoral (subcutaneous) adipose tissue, as measured by hip circumference, in the etiology of EAC. In contrast, our study does not provide support for an association of general obesity with both gastric cardia and gastric non-cardia carcinoma, while the role of abdominal obesity in GCC needs further investigation.

Among the strengths of the present study are its prospective design, the relatively large sample size compared to previous studies and the direct assessment of anthropometric measures. As a limitation, we relied on one baseline measure of anthropometry and were not able to evaluate risk associated with long-term patterns in anthropometrics. However, misclassification is highly unlikely to be differential as anthropometric measurements were taken long before date of diagnosis. Since body fat distribution differs considerably between men and women, sex-specific quintiles of anthropometric measures were used and risk estimates represent an average over men and women. The fact that median values in exposure differ for men and women within quintiles has to be taken into account when interpreting the risk estimates. The number of EAC cases was quite low, resulting at times

Table 3. Hazard Ratios (95% CI) of esophageal, gastric cardia and gastric non-cardia adenocarcinoma across quintiles of anthropometric measures in the EPIC study

		Esophageal adenocarcinoma		Anatomic location of gastric adenocarcinoma			
				Cardia		Non-cardia	
	Median by quintile (men/women)	Cases (*n*)	HR (95% CI)	Cases (*n*)	HR (95% CI)	Cases (*n*)	HR (95% CI)
Height (cm)							
Q1	165/153	27	1.00	26	1.00	69	1.00
Q2	171/158	23	0.81 (0.46–1.42)	46	1.80 (1.10–2.95)	52	1.00 (0.69–1.44)
Q3	175/162	21	0.79 (0.44–1.41)	52	1.99 (1.21–3.25)	47	1.06 (0.72–1.58)
Q4	178/165	32	1.12 (0.65–1.91)	41	1.68 (1.00–2.81)	33	0.84 (0.54–1.32)
Q5	184/170	21	1.01 (0.55–1.85)	28	1.32 (0.75–2.35)	23	0.73 (0.44–1.23)
p trend			0.67		0.52		0.23
Weight (kg)							
Q1	67.0/53.3	17	1.00	33	1.00	50	1.00
Q2	74.3/59.5	25	1.54 (0.82–2.88)	37	1.14 (0.71–1.84)	35	0.68 (0.44–1.06)
Q3	80.0/64.6	23	1.41 (0.74–2.70)	43	1.29 (0.81–2.08)	36	0.67 (0.43–1.06)
Q4	85.9/70.7	26	1.57 (0.82–3.01)	38	1.11 (0.68–1.83)	57	1.02 (0.68–1.55)
Q5	96.0/82.0	33	2.19 (1.14–4.21)	42	1.26 (0.75–2.10)	46	0.84 (0.53–1.32)
p trend			0.03		0.48		0.94
BMI (kg/m^2)							
Q1	22.2/20.5	15	1.00	31	1.00	36	1.00
Q2	24.5/22.7	22	1.30 (0.67–2.52)	37	1.09 (0.68–1.77)	36	0.77 (0.48–1.22)
Q3	26.2/24.6	24	1.36 (0.71–2.62)	48	1.37 (0.87–2.17)	33	0.61 (0.38–0.99)
Q4	28.0/27.1	30	1.76 (0.93–3.31)	41	1.20 (0.74–1.94)	49	0.78 (0.50–1.22)
Q5	31.1/31.6	33	2.15 (1.14–4.05)	36	1.17 (0.71–1.92)	70	0.99 (0.64–1.54)
P trend			0.004		0.53		0.41
Waist circumference (cm)							
Q1	82.5/67.0	7	1.00	22	1.00	25	1.00
Q2	89.0/73.0	22	2.78 (1.18–6.54)	31	1.20 (0.69–2.09)	25	0.81 (0.46–1.42)
Q3	94.0/78.0	20	2.47 (1.03–5.92)	40	1.41 (0.83–2.40)	33	0.89 (0.52–1.52)
Q4	99.0/85.0	26	3.19 (1.36–7.49)	42	1.52 (0.89–2.58)	66	1.58 (0.97–2.57)
Q5	108.0/96.0	39	5.08 (2.21–11.7)	45	1.59 (0.93–2.73)	55	1.14 (0.68–1.91)
p trend			<0.0001		0.06		0.12
Hip circumference (cm)							
Q1	93.0/91.0	16	1.00	39	1.00	34	1.00
Q2	97.0/96.0	26	1.64 (0.87–3.08)	29	0.77 (0.47–1.25)	34	1.01 (0.62–1.63)
Q3	100.5/100.0	30	1.82 (0.98–3.41)	42	0.86 (0.55–1.35)	43	0.94 (0.59–1.50)
Q4	104.0/105.0	15	0.88 (0.43–1.83)	35	0.90 (0.55–1.45)	53	1.28 (0.81–2.02)
Q5	110.0/113.0	27	1.76 (0.91–3.41)	35	0.95 (0.58–1.55)	40	0.81 (0.49–1.33)
p trend			0.41		0.88		0.61
WHR							
Q1	0.86/0.71	9	1.00	17	1.00	14	1.00
Q2	0.91/0.75	11	0.95 (0.39–2.31)	24	1.07 (0.57–2.01)	31	1.68 (0.89–3.17)
Q3	0.94/0.78	20	1.76 (0.79–3.92)	48	2.05 (1.17–3.60)	52	2.20 (1.20–4.00)
Q4	0.97/0.82	28	2.82 (1.30–6.11)	34	1.64 (0.90–2.98)	43	1.90 (1.02–3.54)
Q5	1.02/0.88	46	3.94 (1.87–8.31)	57	2.18 (1.24–3.83)	64	2.12 (1.16–3.89)
p trend			<0.0001		0.002		0.04

Table 3. Hazard Ratios (95% CI) of esophageal, gastric cardia and gastric non-cardia adenocarcinoma across quintiles of anthropometric measures in the EPIC study (Continued)

		Esophageal adenocarcinoma		Anatomic location of gastric adenocarcinoma			
				Cardia		Non-cardia	
	Median by quintile (men/women)	Cases (*n*)	HR (95% CI)	Cases (*n*)	HR (95% CI)	Cases (*n*)	HR (95% CI)
WHtR							
Q1	0.47/0.41	6	1.00	20	1.00	20	1.00
Q2	0.51/0.45	18	2.42 (0.95–6.14)	33	1.37 (0.78–2.39)	30	1.07 (0.60–1.90)
Q3	0.54/0.48	22	2.83 (1.13–7.11)	40	1.57 (0.91–2.72)	26	0.74 (0.41–1.34)
Q4	0.57/0.53	35	4.80 (1.97–11.7)	49	2.00 (1.16–3.44)	60	1.44 (0.84–2.47)
Q5	0.63/0.60	33	5.21 (2.10–13.0)	38	1.78 (1.00–3.18)	68	1.36 (0.77–2.38)
p trend			<0.0001		0.03		0.06

Hazard ratios are derived from Cox proportional hazards regression stratified by age at recruitment and center, and adjusted for sex, education (none/primary, technical/professional, secondary school, university, not specified), smoking (lifelong non-smoking, former smoking with quitting ≥10 years, former smoking with quitting <10 years, current smoking with <15 cigarettes/day, current smoking with 15–24, current smoking with ≥25 cigarettes/day, current smoking other than cigarettes combined with smoking with unknown quantity, and missing), alcohol consumption status (yes/no), alcohol consumption (g/day), physical activity (inactive, moderately inactive, moderately active, active, unknown), red meat, processed meat, vegetables, citrus and non-citrus fruits. Models for weight, BMI, waist, hip and WHR were adjusted for height (continuous) and models for height were adjusted for BMI (continuous).
Quintiles of anthropometric measures represent sex-specific quintiles.
p value for trend was estimated based on the median value of each quintile modeled as continuous variable using the Wald chi-square statistic.

in wide confidence intervals. However, risk estimates were strong and consistent for all obesity measures displaying a clear and indisputable picture of the positive association. Finally, etiology and pathophysiology are known to differ between histologic subtypes of gastric cancer,[32] nevertheless, case numbers of histologic type by anatomic subtype were too low for stratified analyses and collaborative efforts of multiple prospective studies may be necessary to obtain an adequate sample size. Similarly, due to low case numbers among women we were not able to evaluate gender differences.

The present study provides further support for the hypothesis generated by our previous observation[12] and the small number of prospective studies[13,14,33] that abdominal obesity may be a better predictor of EAC risk than general obesity, an observation that has already been reported for other diseases.[7–11] After mutual adjustment of BMI and measures of abdominal obesity, BMI was not associated with EAC, while higher WC showed strongly and significantly increased risks. Similar observations have been reported for Barrett's esophagus (BE),[33–36] a well-known precursor of EAC.

The null result for general obesity in relation to GNCC corroborates the already existing evidence on a lack of association.[5] We also did not observe an association between general obesity and GCC which, at first glance, contradicts the conclusion of the recent meta-analysis.[5] However, the overall result of that meta-analysis appeared to be driven by studies based on self-reported height and weight describing noticeably stronger associations than studies based on measured anthropometry which compare favorably with our finding.[5] The difference in strength of association according to anthropometric assessment suggests that the higher risk estimates found in studies relying on self-reported data may have resulted from misclassification of BMI due to misreported weight and height.[18] For colorectal cancer, it was recently observed that BMI based on self-reported weight and height resulted in higher relative risks than BMI based on measured anthropometry among women.[6]

Our study suggests a role of abdominal obesity in the etiology of GCC. Of the two prospective studies on abdominal obesity and GCC,[13,14] one study including 54 GCC cases did not find a larger anterior–posterior diameter to be a substantial risk factor,[14] while the NIH-AARP study based on 191 GCC observed a significantly higher risk with WC,[13] which compares well with our observation. Currently, evidence on abdominal obesity and GCC is sparse and further studies are needed to corroborate a potential effect of abdominal fat accumulation.

It is of note that associations were notably stronger for measures of abdominal obesity in relation to EAC than GCC, demonstrating abdominal obesity as a robust, indisputable risk factor for EAC but less so for GCC. This observation has been made in other studies[37] but its reasons remain subject to speculation. One biological pathway thought to underlie the association of (abdominal) obesity with EAC is *via* gastro-esophageal reflux disease (GERD) due to enhanced intra-abdominal pressure predisposing to BE and finally leading to EAC.[22] Unlike the clear association between GERD and EAC, the link between GERD and GCC is less strong or even absent,[37] which may partially explain the stronger association found for abdominal obesity and EAC compared to GCC. The underlying pathogenesis of GCC is understudied, though a recent study gave new

Table 4. Hazard ratios (95% CI) for the association of mutually adjusted anthropometric measures with esophageal, gastric cardia and gastric non-cardia adenocarcinoma across quintiles of anthropometric measures in the EPIC study

	HR (95% CI)		
	Esophageal adenocarcinoma	Gastric cardia adenocarcinoma	Gastric non-cardia adenocarcinoma
BMI (kg/m^2) adjusted for WHR			
Q1	1.00	1.00	1.00
Q2	1.42 (0.78–2.58)	1.08 (0.69–1.69)	0.73 (0.46–1.16)
Q3	1.11 (0.59–2.08)	0.94 (0.59–1.50)	0.57 (0.35–0.93)
Q4	1.32 (0.72–2.42)	1.11 (0.70–1.76)	0.73 (0.47–1.15)
Q5	1.19 (0.63–2.22)	0.85 (0.51–1.42)	0.86 (0.56–1.34)
p value for trend	0.8	0.63	0.99
Waist circumference (cm) adjusted for BMI			
Q1	1.00	1.00	1.00
Q2	2.52 (1.15–5.54)	1.52 (0.86–2.68)	1.16 (0.72–1.88)
Q3	1.89 (0.83–4.29)	1.19 (0.66–2.16)	1.23 (0.76–1.99)
Q4	2.42 (1.09–5.38)	1.43 (0.80–2.54)	1.43 (0.88–2.30)
Q5	3.76 (1.72–8.22)	1.91 (1.09–3.37)	1.25 (0.75–2.08)
p value for trend	0.001	0.03	0.27
Waist circumference (cm) adjusted for hip circumference			
Q1	1.00	1.00	1.00
Q2	1.03 (0.42–2.49)	1.31 (0.72–2.38)	1.88 (1.00–3.55)
Q3	1.66 (0.74–3.74)	1.69 (0.96–2.99)	2.41 (1.32–4.40)
Q4	2.65 (1.23–5.69)	1.71 (0.97–3.03)	2.12 (1.16–3.89)
Q5	4.10 (1.94–8.63)	2.23 (1.28–3.90)	2.41 (1.32–4.40)
p value for trend	<0.0001	0.002	0.01
Hip circumference (cm) adjusted for waist circumference			
Q1	1.00	1.00	1.00
Q2	0.92 (0.56–1.51)	0.83 (0.54–1.27)	1.24 (0.81–1.89)
Q3	0.45 (0.24–0.82)	0.71 (0.45–1.11)	1.06 (0.68–1.66)
Q4	0.48 (0.26–0.87)	0.63 (0.39–1.02)	1.08 (0.69–1.70)
Q5	0.35 (0.18–0.68)	0.68 (0.42–1.13)	0.69 (0.41–1.15)
p value for trend	0.0001	0.07	0.11
WHR adjusted for BMI			
Q1	1.00	1.00	1.00
Q2	1.66 (0.69–3.99)	1.24 (0.68–2.27)	1.81 (1.04–3.16)
Q3	2.22 (0.96–5.10)	1.41 (0.79–2.52)	2.19 (1.28–3.76)
Q4	3.33 (1.50–7.37)	1.85 (1.06–3.23)	1.85 (1.07–3.20)
Q5	4.05 (1.85–8.87)	1.95 (1.12–3.38)	2.05 (1.19–3.52)
p value for trend	<0.0001	0.005	0.02

Hazard ratios are derived from Cox proportional hazards regression stratified by age at recruitment and center, and adjusted for height, sex, education (none/primary, technical/professional, secondary school, university, not specified), smoking (lifelong non-smoking, former smoking with quitting ≥10 years, former smoking with quitting <10 years, current smoking with <15 cigarettes/day, current smoking with 15–24, current smoking with ≥25 cigarettes/day, current smoking other than cigarettes combined with smoking with unknown quantity, and missing), alcohol consumption status (yes/no), alcohol consumption (g/day), physical activity (inactive, moderately inactive, moderately active, active, unknown), red meat, processed meat, vegetables, citrus and non-citrus fruits.
Quintiles are sex-specific. To compensate for the problem of collinearity, quintiles for WC and WHR are based on the residuals from the regression of WC or WHR on BMI, respectively. For BMI, quintiles are based on residuals from the regression of BMI on WHR.
p value for trend was estimated based on the median value of each quintile modeled as continuous variable using the Wald chi-square statistic.
WC, waist circumference. WHR, Waist-to-hip ratio.

insights into the events at the cardia that ultimately may lead to GCC among individuals with larger waist.[38] Among 51 asymptomatic volunteers without *H. pylori* and evidence of traditional reflux, Robertson *et al.* observed chronic inflammation among all individuals, but individuals with a higher WC and higher total abdominal fat (but not intra-abdominal fat) were additionally found to exhibit a greater lengthening of the cardiac mucosa pointing to a mechanical mechanism through increased intra-abdominal pressure.[38] The authors also observed a more proximal extension of gastric acid which was attributed to the higher intra-abdominal pressure and may have favored the expansion of adjacent cardia glands.[38,39] Further studies are needed to elucidate the importance of cardia inflammation and expansion as a precursor to EAC and GCC.[39]

Apart from mechanical mechanisms, accumulating evidence suggests humoral mechanisms to link abdominal obesity with EAC, and maybe also GCC, involving alterations in estrogen signaling, the insulin/insulin-like growth factor I (IGF-I) axis and the secretion of adipokines.[40] In relation to GCC, evidence regarding the role of humoral pathways is scarce though a few studies observed lower plasma adiponectin levels and higher levels of IGF-I in patients with (upper) gastric cancer compared to healthy controls.[40–42]

Our study does not support the result of a recent pooled analysis from the Barret's and Esophageal Adenocarcinoma Consortium (BEACON) reporting an inverse association between body height and EAC among 14 case–control studies.[43] Although the study by Thrift *et al.* is well-conducted using an appealing combination of dry epidemiological data analysis and a Mendelian randomization approach, some limitations may be noted. The dry epidemiological analysis was only adjusted for a few dichotomous confounders and the exposure was self-reported in all individuals which might have led to residual confounding and bias due to (differential) misclassification, respectively. Although confounding is excluded by definition through the application of Mendelian randomization, the results from Mendelian randomization showed wide confidence intervals that included the null value, warranting some caution with regard to definite conclusions (per each 10 cm increase in height OR = 0.73, 95% CI, 0.46–1.15 and OR = 0.63, 95% CI, 0.15–2.63, for men and women, respectively). Nevertheless, the role of height in EAC may deserve further investigation, not least because an inverse association contrasts with numerous previous studies showing a positive association between height and risk of several cancers.[4]

A remarkable finding in relation to EAC and, less pronounced, for GCC is the inverse association of HC that became only apparent after adjusting for WC, which underscores the usefulness of jointly including WC and HC in the assessment of obesity-related health risk rather than focusing solely on WHR. An inverse association with HC after controlling for WC has already been reported in relation to heart disease, Type 2 diabetes and mortality,[29,31,44] and our observation encourages future efforts into elucidating the role of HC in chronic diseases, including EAC. Underlying biological mechanisms for a protective effect of a larger hip with given WC are currently not well understood. Higher gluteofemoral fat, as reflected by larger hips, has been related to a more beneficial adipokine profile and may further determine metabolic health by trapping excess fatty acids.[45] In particular, subcutaneous adipose tissue may act as a buffer for the daily influx of dietary lipids, protecting other tissues from a lipid overflow with related lipotoxicity, thereby acting as a protective "metabolic sink."[45,46] On that note, the gluteofemoral fat accumulation has been associated with an elevated lipoprotein lipase activity, indicating a differential local handling of fatty acid uptake and release.[45]

In conclusion, our study demonstrates that abdominal, rather than general, obesity is a strong and robust risk factor for EAC and also provides new evidence for a protective effect of gluteofemoral (subcutaneous) adipose tissue in EAC. While the role of abdominal obesity in gastric cardia cancer needs further investigation, general obesity does not seem to be a risk factor for this cancer site.

Epidemiology

References

1. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. *Ann Oncol* 2012;23:3155–62.
2. Camargo MC, Anderson WF, King JB, et al. Divergent trends for gastric cancer incidence by anatomical subsite in US adults. *Gut* 2011;60: 1644–9.
3. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607–15.
4. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical actitivity, and the prevention of cancer: a global perspective. Washington DC: AICR, 2007.
5. Chen Y, Liu L, Wang X, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. *Cancer Epidemiol Biomarkers Prev* 2013;22:1395–408.
6. Park JY, Mitrou PN, Keogh RH, et al. Self-reported and measured anthropometric data and risk of colorectal cancer in the EPIC-Norfolk study. *Int J Obes (Lond)* 2012;36:107–18.
7. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359: 2105–20.
8. Pischon T, Boeing H, Weikert S, et al. Body size and risk of prostate cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2008;17:3252–61.
9. Wang Y, Rimm EB, Stampfer MJ, et al. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005;81:555–63.
10. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case–control study. *Lancet* 2005;366:1640–9.
11. Song X, Jousilahti P, Stehouwer CD, et al. Comparison of various surrogate obesity indicators as predictors of cardiovascular mortality in four European populations. *Eur J Clin Nutr* 2013;67: 1298–302.
12. Steffen A, Schulze MB, Pischon T, et al. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2009;18:2079–89.
13. O'Doherty MG, Freedman ND, Hollenbeck AR, et al. A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. *Gut* 2012;61:1261–8.

14. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev* 2008; 17:352–8.
15. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;5:1113–24.
16. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997;26 (Suppl 1): S6–S14.
17. Haftenberger M, Lahmann PH, Panico S, 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 Nutr* 2002;5:1147–62.
18. Spencer EA, Appleby PN, Davey GK, et al. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. *Public Health Nutr* 2002;5:561–5.
19. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr* 2003;6:407–13.
20. Malfertheiner P, Selgrad M. Helicobacter pylori infection and current clinical areas of contention. *Curr Opin Gastroenterol* 2010;26:618–23.
21. Islami F, Kamangar F. Helicobacter pylori and esophageal cancer risk: a meta-analysis. *Cancer Prev Res (Phila)* 2008;1:329–38.
22. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143:199–211.
23. Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol* 2012;23:1403–15.
24. Tian W, Zhao Y, Liu S, et al. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. *Eur J Cancer Prev* 2010;19:288–98.
25. Jacobs EJ, Thun MJ, Bain EB, et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J Natl Cancer Inst* 2007;99:608–15.
26. Carneiro F, Moutinho C, Pera G, et al. Pathology findings and validation of gastric and esophageal cancer cases in a European cohort (EPIC/EURGAST). *Scand J Gastroenterol* 2007;42:618–27.
27. Expert panel on the Identification E, and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr* 1998;68: 899–917.
28. Hu FB. Obesity epidemiology. New York: Oxford University Press, Inc., 2008.
29. Cameron AJ, Magliano DJ, Soderberg S. A systematic review of the impact of including both waist and hip circumference in risk models for cardiovascular diseases, diabetes and mortality. *Obes Rev* 2013;14:86–94.
30. Neamat-Allah J, Wald D, Husing A, et al. Validation of anthropometric indices of adiposity against whole-body magnetic resonance imaging—a study within the German European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts. *PLoS One* 2014;9:e91586.
31. Cameron AJ, Magliano DJ, Shaw JE, et al. The influence of hip circumference on the relationship between abdominal obesity and mortality. *Int J Epidemiol* 2012;41:484–94.
32. Wong H, Yau T. Molecular targeted therapies in advanced gastric cancer: does tumor histology matter? *Therap Adv Gastroenterol* 2013;6:15–31.
33. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013;11:1399–412 e7.
34. El-Serag HB, Hashmi A, Garcia J, Richardson P, Alsarraj A, Fitzgerald S, Vela M, Shaib Y, Abraham NS, Velez M, Cole R, Rodriguez MB, et al. Visceral abdominal obesity measured by CT scan is associated with an increased risk of Barrett's oesophagus: a case-control study. *Gut* 2014; 63:220–9.
35. Kramer JR, Fischbach LA, Richardson P, et al. Waist-to-hip ratio, but not body mass index, is associated with an increased risk of Barrett's esophagus in white men. *Clin Gastroenterol Hepatol* 2013;11:373–81 e1.
36. Rubenstein JH, Morgenstern H, Appelman H, et al. Prediction of Barrett's esophagus among men. *Am J Gastroenterol* 2013;108:353–62.
37. Olefson S, Moss SF. Obesity and related risk factors in gastric cardia adenocarcinoma. Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association 2015;18:23–32.
38. Robertson EV, Derakhshan MH, Wirz AA, et al. Central obesity in asymptomatic volunteers is associated with increased intrasphincteric acid reflux and lengthening of the cardiac mucosa. *Gastroenterology* 2013;145:730–9.
39. Quante M, Abrams JA, Wang TC. The rapid rise in gastroesophageal junction tumors: is inflammation of the gastric cardia the underwater iceberg? *Gastroenterology* 2013;145:708–11.
40. Aleman JO, Eusebi LH, Ricciardiello L, et al. Mechanisms of obesity-induced gastrointestinal neoplasia. *Gastroenterology* 2014;146:357–73.
41. Ishikawa M, Kitayama J, Kazama S, et al. Plasma adiponectin and gastric cancer. *Clin Cancer Res* 2005;11:466–72.
42. Franciosi CM, Piacentini MG, Conti M, et al. IGF-1 and IGF-1BP3 in gastric adenocarcinoma. Preliminary study. *Hepatogastroenterology* 2003; 50:297–300.
43. Thrift AP, Risch HA, Onstad L, et al. Risk of esophageal adenocarcinoma decreases with height, based on consortium analysis and confirmed by mendelian randomization. *Clin Gastroenterol Hepatol* 2014;12:1667–76 e1.
44. Heitmann BL, Lissner L. Hip Hip Hurrah! Hip size inversely related to heart disease and total mortality. *Obes Rev* 2011;12:478–81.
45. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond)* 2010;34:949–59.
46. Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002;45:1201–10.