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

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Abstract

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. 124 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.

Keywords

General obesity; abdominal obesity; Body Mass Index; Waist circumference; gastric cancer; esophageal cancer

Introduction

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 *H. 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.

Materials and Methods

Study population

The EPIC study is a multi-center 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 0.1kg and 0.1 or 0.5cm, respectively, with subjects wearing no shoes, as described in detail previously.¹⁷ Waist circumference 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/m²), 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 (hrs/week, coded in four categories: none, 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 obesity²⁰ 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 $\geq 30\text{kg/m}^2$ 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 $\geq 10\text{y}$, former smoking ceased $<10\text{y}$, current smoking with $<15\text{ cig/d}$, current smoking with 15-24 cig/d, current smoking with $\geq 25\text{ cig/d}$, and current smoking with unknown quantity or smoking other than cigarettes, missing), alcohol consumption at recruitment (yes/no) and amount of alcohol (g/d), physical activity (inactive, moderately inactive, moderately active, active, and missing), and intake of red and processed meat, vegetables, citrus and non-citrus fruits (g/d). 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 Waist circumference reflects both visceral and subcutaneous adipose tissue, while HC provides a more specific measure of subcutaneous gluteofemoral 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 2-tailed and $P < 0.05$ was considered statistically significant. Analyses were performed using SAS, version 9.1 (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, 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 towards 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 two 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 esophageal adenocarcinoma. 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 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 observation¹² 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 WC¹³ 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 studies³⁷ 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 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 waist circumference 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 Barrett'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 10cm 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.

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List of 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

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Novelty and impact

Previous studies often relied on self-reported anthropometry and mainly investigated general obesity (BMI) in relation to gastric and esophageal adenocarcinoma. Contrary to previous studies, our study based on measured anthropometry, shows that general obesity is not a risk factor for gastric cardia cancer, while the role of abdominal obesity (waist circumference) needs further exploration. Interestingly, our study provides new evidence on the possibly protective effect of gluteofemoral adipose tissue (hip circumference) for esophageal adenocarcinoma.

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

Country	Cohort size (n)	Person-years	EAC ^a	Total ^b	Gastric cancer				Mean (SD) of anthropometric measures					
					Anatomic site		Histology		BMI (kg/m ²)		WC (cm)		WHR	
					Cardia	Non-cardia	Diffuse ^b	Intestinal ^b	Men	Women	Men	Women	Men	Women
France	19810	211532	NA	7	4	1	3	2	NA	23.4 (3.7)	NA	76.6 (9.5)	NA	0.78 (0.07)
Italy	44195	496096	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	39612	477769	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	73816	820195	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	36487	431050	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	25908	246543	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	48139	476345	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	48510	636765	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	54979	601070	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	391456	4397365	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)	0.79 (0.07)

^aEAC, Esophageal adenocarcinoma. France and Greece were excluded from the analysis on EAC due to incomplete case identification routines for this cancer site.

^bThere 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 WHR among men and women in the EPIC study (n=391,456)

Characteristic	BMI quintiles (median) among men (n=141,122)					BMI quintiles (median) among women (n=250,334)				
	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, 10y ago	9	11	13	15	17	8	9	9	8	8
Former, < 10y ago	16	22	23	24	23	13	14	14	13	11
Current, <15 cig/d	9	8	7	7	7	9	9	8	7	5
15 – 24 cig/d	10	8	8	8	8	6	6	6	6	4
25 cig/d	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
Alcohol consumer (%)	94	94	94	93	92	90	89	86	81	72
Baseline alcohol intake (g/d)*	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)*	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/1000kcal)*	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)

Characteristic	BMI quintiles (median) among men (n=141,122)					BMI quintiles (median) among women (n=250,334)				
	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)
Vegetable (g/1000kcal)*	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)*	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)*	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.

* Median and interquartile range. For alcohol, among consumers only.

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

	Median by quintile (men/women)	Esophageal adenocarcinoma		Anatomic location of gastric adenocarcinoma			
		Cases (n)	HR (95% CI)	Cardia		Non-cardia	
				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/m²)							
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			<.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)

	Median by quintile (men/women)	Esophageal adenocarcinoma		Anatomic location of gastric adenocarcinoma			
		Cases (n)	HR (95% CI)	Cardia		Non-cardia	
				Cases (n)	HR (95% CI)	Cases (n)	HR (95% CI)
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			<.0001		0.002		0.04
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			<.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/d), 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.

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/m²) 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	<.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	<.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/d), 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.