

# Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium

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**Background** Previous studies suggest an association between obesity and oesophageal (OA) and oesophagogastric junction adenocarcinomas (OGJA). However, these studies have been limited in their ability to assess whether the effects of obesity vary by gender or by the presence of gastro-oesophageal reflux (GERD) symptoms.

**Methods** Individual participant data from 12 epidemiological studies (8 North American, 3 European and 1 Australian) comprising 1997 OA cases, 1900 OGJA cases and 11 159 control subjects were pooled. Logistic regression was used to estimate study-specific odds ratios (ORs) and 95% confidence intervals (CIs) for the association between body mass index (BMI, kg/m<sup>2</sup>) and the risk of OA and OGJA. Random-effects meta-analysis was used to combine these ORs. We also investigated effect modification and synergistic interaction of BMI with GERD symptoms and gender.

**Results** The association of OA and OGJA increased directly with increasing BMI (*P* for trend <0.001). Compared with individuals with a BMI <25, BMI ≥40 was associated with both OA (OR 4.76, 95% CI 2.96–7.66) and OGJA (OR 3.07, 95% CI 1.89–4.99). These associations were similar when stratified by gender and GERD symptoms. There was

evidence for synergistic interaction between BMI and GERD symptoms in relation to OA/OGJA risk.

**Conclusions** These data indicate that BMI is directly associated with OA and OGJA risk in both men and women and in those with and without GERD symptoms. Disentangling the relationship between BMI and GERD will be important for understanding preventive efforts for OA and OGJA.

**Keywords** Oesophageal neoplasms, aetiology, risk factors, gastro-oesophageal reflux, obesity, oesophagogastric junction

## Background

The incidence of adenocarcinomas of the oesophagus (OA) has increased >650% in the USA over the past 35 years, the steepest increase of any cancer during this period.<sup>1,2</sup> To a lesser extent, the incidence of the anatomically linked oesophagogastric junction adenocarcinoma (OGJA) has also risen.<sup>3</sup> Five-year survival for these cancers continues to be low despite improvements in treatment modalities and supportive care.<sup>4,5</sup> Over the past 2 decades, research has focused on identifying risk factors for OA and OGJA, with an ultimate goal of elucidating a strategy to reduce incidence and mortality from these cancers. Any potentially effective prevention programme will need to take into consideration that the incidence varies dramatically by race and gender, with White men comprising 80% of individuals with OA and OGJA.<sup>6,7</sup>

Consistently documented risk factors for these tumours include symptoms of gastro-oesophageal reflux (GERD)<sup>8,9</sup> and male gender.<sup>6</sup> Increasing body mass index (BMI) has also been associated with OA and OGJA tumours (reviewed in the article by Lagergren<sup>10</sup>), and perhaps GERD (reviewed in the articles by El-Serag<sup>11</sup> and Friedenberg<sup>12</sup>). Higher BMI (kg/m<sup>2</sup>) may directly increase the propensity for GERD<sup>13,14</sup>; android obesity may increase intra-abdominal pressure, distort the lower oesophageal sphincter and increase the likelihood of hiatal hernia. Several recent lines of evidence also suggest that BMI may increase the risk of OA, its precursor lesion Barrett's oesophagus, and OGJA independently of GERD.<sup>13–19</sup> Potential indirect mechanisms of these associations include the idea that differences in adipose distribution between men and women may partly explain the much higher incidence of these cancers in men.<sup>20,21</sup> Men typically acquire android fat patterns, characterized by central abdominal fat deposits, whereas women typically develop gynoid forms, with fat deposits on the hips and thighs<sup>21,22</sup>; android (visceral) fat is known to be more metabolically active<sup>20</sup> relative to gynoid.<sup>23,24</sup> Disentangling these relationships will be important for primary prevention of these tumours, but so far these efforts have been limited by small case numbers of participants in individual studies. The International Barrett's and Oesophageal Adenocarcinoma Consortium

(BEACON, <http://beacon.tlvnet.net/>) provided data from 12 studies to assess the effect of increasing BMI on OA and OGJA risk. The large size of the consortium also enabled the assessment of potential effect modification by GERD and gender.

## Methods

### Study population

This combined analysis included participants in OA and OGJA studies who contributed their data to the International BEACON. BEACON was formed in 2005 by an international group of investigators in collaboration with the US National Cancer Institute. The consortium consists of completed or ongoing case-control and cohort studies of OA, OGJA and/or Barrett's oesophagus and has a primary aim to provide an open scientific forum for epidemiological research into the aetiology and prevention of these diseases by facilitating the sharing of data across population-based studies. Therefore, rather than relying on a meta-analytical approach with published risk estimates, which often have different variable definitions and statistical models, BEACON enables pooled analyses of individual participant data from population-based studies using a standard model, after harmonization of variable definitions and common confounders.

Data from 10 case-control studies, conducted between 1988 and 2005, and two cohort studies, with recruitment between 1964 and 1996, were available through BEACON at the time of analysis. Of the 12 studies, 8 were conducted in North America,<sup>25–31</sup> 3 in Europe<sup>18,32,33</sup> and 1 in Australia.<sup>19</sup> Detailed descriptions of case ascertainment procedures can be found in study-specific publications.<sup>18,19,23,25–30,32–34</sup>

### Cases

The main outcomes were (i) OA, (ii) OGJA and (iii) OA and OGJA grouped together (all adenocarcinomas). For each study, determination of case participant eligibility was based on pathology reports and/or review of medical records. In both cases, determination of histology and site of tumour origin of OA vs OGJA was made based on radiology, surgery, or endoscopy reports and review of pathology or reports.

### Control subjects

Control subjects were identified from the populations from which the cases arose. For the cohort studies, a nested case-control approach was used, where a random sample of control subjects for each case was selected. The case-control ratio was 1:4 for the National Institutes of Health-American Association of Retired Persons (formerly known as American Association of Retired Persons) cohort study and 1:8 for the Kaiser Permanente cohort.<sup>27</sup>

Inclusion criteria and the pooling strategy have been described elsewhere.<sup>35</sup> In total, 4214 cases and 13 750 control subjects were available for pooling. Cases included 2138 OAs and 2076 OGJAs. We excluded participants for whom either height or weight was missing (422 control subjects 49 OA, 45 OGJA). The analysis was limited to non-Hispanic White participants because the BEACON pooled data set had too few African American (12 OA, 35 OGJA, 1226 control subjects), Hispanic (55 OA, 48 OGJA, 442 control subjects) or other-ethnicity participants (23 OA, 45 OGJA, 449 control subjects) for meaningful analysis. In addition, we excluded individuals for whom race was unknown (52 control subjects, 2 OA, 3 OGJA). Analyses were thus based on 3897 cases (1997 OA, 1900 OGJA) and 11 159 control subjects.

In Table 1, we present basic descriptive characteristics of the case and control populations for each study. The conduct of individual studies and contribution of data for consortial analyses in BEACON were approved by the relevant institutional review or research ethics boards for each study.

### Study variables

BMI was based on self-reported adult height and weight for all studies, although the exposure date in relation to cancer diagnosis varied across studies. Consequently, we used usual adult weight.<sup>15,28,30,34</sup> If usual adult weight was unavailable, we used weight 1 year,<sup>19,26,29</sup> 5 years<sup>32</sup> or 20 years before interview.<sup>18</sup> One study ascertained weight at age 20 years and maximum adult weight (excluding pregnancies), for which we used the latter weight, assuming it more accurately reflected usual adult weight.<sup>28</sup> For the two nested case-control studies, we used weight at cohort entry.<sup>23,27</sup> BMI was categorized into an ordinal variable with five groups based on WHO criteria<sup>36</sup>: BMI <25, BMI 25–29.9, BMI 30–34.9, BMI 35–39.9 and BMI ≥40. Additionally, we defined a combined obese group (BMI ≥30). Fewer than 1% of participants had a BMI <19, and these were included in the referent category of BMI <25.

GERD symptoms, where available,<sup>19,25,26,32</sup> were defined as a history of reflux or heartburn 1 year before diagnosis for cases and 1 year before interview for control subjects. Heartburn symptoms solicited included 'burning or aching pain behind the breastbone not due to heart problems'. Reflux symptoms

solicited included 'sour taste from acid, bile or contents of the stomach'.

Other covariables included in analyses were age (categorized as <50, 50–59, 60–69 and ≥70 years), gender, education (less than high school, high school or more), cigarette smoking (categorized as <15, 15 to <30, 30 to <45 and ≥45 pack-years derived from dividing the number of cigarettes smoked by 20 and multiplying by the total number of years smoked), regular alcohol consumption (yes/no) and, where available,<sup>15,18,26,32</sup> *Helicobacter pylori* colonization (yes/no).

### Statistical analyses

Using each study's individual-level data and covariates, we estimated study-specific odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between BMI categories and adenocarcinoma outcomes using logistic regression models. We also estimated ORs and 95% CIs per unit increase in BMI as a continuous covariate. All models were adjusted for age, gender, education, cigarette smoking, GERD (where available) and study-specific variables, such as study centre,<sup>35</sup> as applicable. Study-specific estimates were subsequently combined using random-effects meta-analytic models. The results from fixed-effects models were similar; however, we believe that random-effects models are more appropriate for the current analyses.<sup>37</sup> To estimate heterogeneity, we computed the  $I^2$  statistic.<sup>38</sup> The  $I^2$  statistic ranges from 0 to 100%, where  $I^2 = 0$  indicates no observed heterogeneity and larger values indicate increasing heterogeneity.

We also investigated the relationship between BMI and cancer using spline models<sup>39</sup> to plot the relationship on a continuous scale. Restricted cubic spline models allow for easy visualization of non-linear relationships between an exposure and an outcome<sup>40,41</sup>—in this case, BMI and OA/OGJA. These analyses were adjusted for age (categorical), gender, pack-years of cigarette smoking (categorical), education (harmonized, dichotomous: less than high school, high school or more) and study site/centre (categorical) using the pooled data set of individual patient data. Results from spline models were plotted using a linear scale on the x-axis for BMI and a logarithmic (base 10) scale on the y-axis for the OR. Plots were constructed for OA and OGJA overall and also for subgroups defined by gender and GERD symptoms.

We assessed whether there was evidence for effect modification—i.e. whether the effect of single exposure (BMI) on cancer risk (OA/OGJA) varied over strata of a second variable (an effect modifier).<sup>42–44</sup> The variables, age, gender and GERD symptoms were tested as potential effect modifiers of the association between BMI and cancer. We evaluated the strength of potential effect modification by addition of product terms to study-specific logistic regression models followed by random-effects meta-analysis.

**Table 1** BEACON studies available for analysis of body mass index and adenocarcinomas of the oesophagus and oesophagogastric junction

Name	Country of Study	Period of Recruitment	Cases					Controls				
			OA (n)	OGJA (n)	AA (n)	Age [mean (SD)]	Male (%)	BMI [mean (SD)]	n	Age [mean (SD)]	Male (%)	BMI [mean (SD)]
Australian Cancer Study <sup>a</sup>	Australia	2001–05	344	403	747	63.5 (9.7)	88.5	28.7 (5.0)	1447	60.5 (11.7)	65.8	26.9 (4.6)
Nova Scotia Barrett Esophagus Study <sup>a</sup>	Canada	2001–03	55		55	64.2 (9.7)	89.5	27.5 (5.6)	99	54.7 (13.7)	64.7	28.9 (5.9)
Factors Influencing the Barrett's Adenocarcinoma Relationship Study <sup>a</sup>	Ireland	2002–04	130	92	222	64.2 (11.1)	85.2	28.6 (4.8)	259	63.0 (12.8)	84.6	27.0 (3.9)
Swedish Esophageal Cancer Study <sup>a</sup>	Sweden	1995–97	189	262	451	65.3 (9.9)	86.0	25.6 (3.9)	816	66.0 (10.0)	82.8	23.9 (2.8)
United Kingdom Study of Esophageal Cancer in Women <sup>a</sup>	United Kingdom	1993–96	72		72	65.3 (8.7)	0.0	29.8 (6.9)	72	65.9 (8.8)	0.0	26.9 (4.8)
Kaiser Permanente Multiphasic Health Checkup Study <sup>b</sup>	United States	1964–73	86	85	171	46.2 (11.2)	80.6	26.2 (3.6)	2021	47.5 (11.0)	74.6	25.2 (3.7)
Larynx/Esophagus/Oral Cavity Study <sup>a</sup>	United States	1983–90	129	154	283	61.1 (9.3)	89.6	26.5 (4.4)	694	59.8 (10.0)	69.9	25.9 (4.0)
Los Angeles Multi-ethnic Study <sup>b</sup>	United States	1992–97	168	205	373	60.9 (9.8)	86.7	27.0 (5.2)	834	58.7 (11.5)	73.7	25.8 (4.4)
Nebraska Health Study II <sup>a</sup>	United States	1988–93	123	44	167	68.3 (12.4)	86.6	26.4 (3.7)	489	68.3 (17.6)	56.6	25.2 (4.5)
NIH-AARP Study <sup>b</sup>	United States	1995–96	366	296	662	63.7 (5.0)	90.9	28.2 (4.8)	3083	62.1 (5.3)	60.2	27.0 (4.7)
Population Health Study <sup>a</sup>	United States	1986–89	58	113	171	62.5 (9.6)	100.0	26.7 (3.8)	722	61.3 (11.0)	100.0	25.2 (3.2)
US Multi-Center Study <sup>a</sup>	United States	1993–95	277	246	523	63.7 (10.9)	84.5	26.1 (4.2)	623	62.8 (10.7)	79.9	24.9 (3.4)
<b>Total</b>			<b>1997</b>	<b>1900</b>	<b>3897</b>	<b>62.7 (10.3)</b>	<b>86.3</b>	<b>27.3 (4.8)</b>	<b>11 159</b>	<b>58.9 (12.0)</b>	<b>71.9</b>	<b>26.0 (4.3)</b>

<sup>a</sup>Case-control study.

<sup>b</sup>Cohort study with a nested case-control set selected for BEACON.

OA = oesophageal adenocarcinoma; OGJA = oesophagogastric junction adenocarcinoma; AA = all adenocarcinomas (OA and OGJA); BMI = body mass index; SD = standard deviation.

We also assessed whether there was evidence of interaction (synergism or departure from additivity)<sup>42–44</sup> i.e. whether the joint effect of two exposures (BMI and another) had greater effects on the risk of OA and OGJA than would be expected from the independent effects of each exposure. Dichotomous variables tested for departure from additivity with BMI (dichotomized at  $<27.5$  and  $\geq 27.5$ ) were cigarette smoking, gender, alcohol, GERD symptoms and *H. pylori* colonization. For each combination of variables, we generated four exposure categories. These variables were modelled in the pooled data set using logistic regression adjusted for age (categorical), gender, BMI (continuous), heartburn or reflux (if unavailable for a study, all individuals were recoded to a missing category and were excluded from the heartburn/reflux/heartburn-or-reflux–BMI interaction models), education (harmonized, dichotomous: less than high school, high school or more) and study site/centre (categorical). The output from these models was used to estimate three interaction statistics: interaction contrast ratio (ICR), attributable proportion (AP) and synergy index (S). When the ICR and  $AP \neq 0$ , and  $S \neq 1$ , there is evidence for departure from additivity (interaction). ICR is the excess risk due to interaction relative to the risk without either exposure. AP is the proportion of disease attributable to interaction among individuals with both exposures. S is the ratio of the observed excess risk in individuals exposed to both factors relative to the expected excess risk assuming that both exposures are independent risk factors (i.e. under the assumption of no additive interaction). CIs for these metrics were estimated using the delta method.<sup>45</sup> All analyses were conducted using STATA software version 11 (StataCorp LP, College Station, TX).

## Results

Descriptive characteristics of case and control groups by study are shown in Table 1. The number of cases varied between studies from 72 to 747, and the mean ages were generally 63–65 years, although the age was much younger in the Kaiser Permanente Multiphasic Health Check-up Study because of its design (cohort). The UK study was of women only, and the Population Health Study was of men only, but all other studies were composed of, on average, 86% men and 14% women. The mean BMI for cases was generally higher than that for control subjects with overall means being 27.2 and 26.0, respectively.

Table 2 shows adjusted summary ORs for the associations between BMI and the risk of OA, OGJA and all adenocarcinomas among men and women combined. Compared with BMI  $<25$ , the increase in OA risk in individuals with BMI 25–29.9 was 1.54 (95% CI 1.26–1.88), a risk that increased to  $>2$ -fold in individuals with BMI 30–34.9 (OR 2.39, 95% CI 1.86–3.06) or BMI 35–39.9 (OR 2.79, 95% CI

1.89–4.12) (Table 2), and almost 5-fold in individuals with BMI  $\geq 40$  (OR 4.76, 95% CI 2.96–7.66). The patterns of association between BMI and these adenocarcinomas were similar in younger ( $\leq 65$  years) and older ( $>65$  years) individuals when stratified by age at diagnosis (data not shown). These results were unaltered when we repeated the analyses, adjusting for GERD, in the five studies with GERD information (data not shown). This monotonic increase in risk was also observed when BMI was evaluated in relation to OGJA and all adenocarcinomas. The associations were slightly stronger with OA than OGJA. Excluding individuals with potential cachexia (BMI  $<18.5$ ) had little effect on the estimates attained.

We evaluated the association between BMI and OA, OGJA and all adenocarcinomas, stratified by GERD symptoms, including heartburn and reflux (Table 3). The pattern and magnitude of associations between BMI and OA, OGJA or all adenocarcinomas were similar in the studies with GERD data available compared with those of all participants (data not shown). A history of GERD symptoms did not materially alter the patterns and magnitude of associations between BMI and cancer. Among individuals with a history of GERD symptoms, overweight status was associated with an  $\sim 50\%$  increase in OA risk relative to BMI  $<25$ . Risk increased linearly with increasing BMI to  $>2$ -fold in individuals with BMI 30–34.9 (OR 2.21, 95% CI 1.44–3.39) and 5-fold in individuals with BMI 35–39.9 (OR 5.84, 95% CI 2.72–12.55). A similar pattern and magnitude of association were also observed among individuals with no history of GERD symptoms. The pattern of association in GERD-stratified analyses was similar for OGJA and the combined grouping of all adenocarcinomas, although the magnitude of association was somewhat stronger in the BMI–OA than the BMI–OGJA analyses.

To determine whether gender was an effect modifier of the observed associations between the exposure, BMI and the outcome OA/OGJA, we conducted analyses stratified by gender (Table 4). Compared with men in the category BMI  $<25$ , those with BMI 25–29.9 were at greater than 60% increased risk of OA (OR 1.63, 95% CI 1.32–2.00), a risk that increased linearly with increasing BMI to  $>4$ -fold (OR 4.47, 95% CI 2.42–8.26) in men with BMI  $\geq 40$ . These patterns of association were similar for OGJA and the combined group of all adenocarcinomas for men, although, again, associations were strongest for OA. This pattern of association between BMI and OA, and a weaker association with OGJA, were also observed among women (Figure 1).

To explore the relationships between BMI and OA/OGJA in men and women further, and the lack of attenuation of the magnitude of the association in individuals with symptomatic GERD (heartburn and reflux), we stratified the spline models by gender and GERD. The relationship between increasing BMI and cancer risk was similar for men and women who

**Table 2** Adjusted summary odds ratios and 95% confidence intervals for the association between body mass index and adenocarcinomas of the oesophagus and oesophagogastric junction among all subjects (men and women combined)

BMI (kg/m <sup>2</sup> )	OA				OGJA				All adenocarcinomas									
	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>	N	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>	N	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>	N
<25.0	4744	577		Referent			4686	663		Referent			4777	1240		Referent		
25.0–29.9	4232	862	1.54	1.26–1.88	55	12	4147	742	1.28	1.13–1.45	0	10	4232	1604	1.41	1.24–1.60	37	12
30.0–34.9	1109	331	2.39	1.86–3.06	42	12	1081	304	2.08	1.75–2.47	0	10	1109	635	2.23	1.83–2.71	41	12
35.0–39.9	273	86	2.79	1.89–4.12	23	11	266	85	2.36	1.75–3.17	0	9	273	171	2.40	1.89–3.04	0	11
≥40	94	41	4.76	2.96–7.66	0	9	91	28	3.07	1.89–4.99	0	8	99	69	3.65	2.50–5.34	0	10
Continuous	10481	1897	1.09	1.06–1.12	76	12	10295	1822	1.07	1.05–1.09	54	10	10481	3719	1.08	1.06–1.10	75	12

Results were adjusted for age (categorical: <50, 50–59, 60–69, ≥70 years), gender, pack-years of smoking (categorical: <15, 15 to <30, 30 to <45, ≥45), education (study-specific) and other study-specific adjustment variables (e.g. study centre, where applicable). Summary odds ratios and 95% confidence intervals were obtained from random-effects models. All 12 studies were included for analysis unless otherwise specified. I<sup>2</sup> estimates variability in results across studies. OA = oesophageal adenocarcinoma; OGJA = oesophagogastric junction adenocarcinoma; AA = all adenocarcinomas (OA and OGJA); BMI = body mass index; OR = odds ratio; N = number of studies in the analysis.

reported symptomatic GERD (Supplementary Figure S1, available as Supplementary data at *IJE* online). Conversely, the relationship appeared attenuated in women compared with the relationship observed in men with no GERD symptoms (Supplementary Figure S2, available as Supplementary data at *IJE* online), although the analysis of women who did not report GERD was based on just 33 OA cases and 357 control subjects.

In analyses testing for interaction (synergism, departure from additivity), we found evidence for synergism between BMI and GERD with respect to OA risk (Table 5). Compared with the referent of no GERD symptoms and low BMI (<27.5), the OR for GERD symptoms and low BMI was 2.28 (1.83–2.84), for no GERD symptoms and high BMI (≥27.5) was 1.26 (0.91–1.74) and for GERD and high BMI was 3.18 (2.45–4.13). The excess risk attributable to the synergistic interaction of GERD and high BMI was estimated to be 0.64 (0.12–1.17), with an AP of OA due to interaction of 0.20 (0.05–0.35).

## Discussion

In this large consortial analysis, we report strong linear relationships between increasing BMI and the risk of OA. There was no evidence of effect modification when stratified by GERD symptoms, which may suggest an indirect proinflammatory route of association between BMI and OA/OGJA exists, as well as direct mechanical effects of android fat. There was putative evidence that gender may modify the relationship between BMI and OA in individuals without a history of GERD symptoms, which also may be interpreted as further evidence for an indirect proinflammatory route of association emanating from highly metabolic visceral fat when direct inflammatory routes (GERD) of pathogenesis do not predominate. Lastly, we found evidence for synergistic effects of BMI and GERD; the risk of cancer in obese individuals with GERD was significantly higher than predicted under an additive model.

Our findings of a strong positive dose–response relationship between BMI and the risk of OA reiterate the fact that this cancer is the primary malignancy associated with obesity.<sup>46</sup> We also found similar, although somewhat weaker, associations for OGJA, and this is consistent with the hypothesis that OGJA represents a heterogeneous set of tumours with less clear origin compared with OA.<sup>47</sup> Our results are compatible with findings from a previous meta-analysis that used published ORs from 14 studies,<sup>48</sup> 6 of them included here,<sup>15,18,26,33,34,49</sup> as well as findings reported by other studies not included in the present analysis.<sup>50–56</sup> Importantly, our study extends these results through the use of pooled individual participant data and harmonized variables and statistical models while also enabling analyses of effect modification and interaction. Overall, our findings support the hypothesis

**Table 3** Adjusted odds ratios and 95% confidence intervals for the association between body mass index and risk of oesophageal adenocarcinoma, oesophago-gastric junction adenocarcinoma and all adenocarcinomas, stratified by heartburn and gastro-oesophageal reflux

BMI (kg/m <sup>2</sup> )	No GERD					GERD				
	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>
Oesophageal adenocarcinoma										
<25.0	614	94		Referent		705	180		Referent	
25.0–29.9	532	95	1.12	0.80–1.58	0	739	282	1.48	1.07–2.05	40
30.0–34.9	136	37	1.85	0.91–3.73	48	224	129	2.21	1.44–3.39	37
35.0–39.9	47	15	2.08	1.00–4.30	0	62	36	2.95	1.15–7.59	49
≥40	10	4	6.45 <sup>a</sup>	1.60–25.99	100	20	18	5.84	2.72–12.55	0
Continuous	1341	246	1.07	1.03–1.11	0	1750	645	1.08	1.03–1.14	71
Oesophago-gastric junctional adenocarcinoma										
<25.0	614	128		Referent		705	172		Referent	
25.0–29.9	532	136	1.22	0.77–1.95	56	739	239	1.16	0.87–1.56	24
30.0–34.9	136	54	2.08	1.36–3.19	0	224	116	1.91	1.4–2.6	0
35.0–39.9	47	14	1.49	0.74–2.98	0	62	40	3.65	1.58–8.46	50
≥40	12	4	3.20 <sup>b</sup>	0.89–11.52	0	20	11	2.64	1.16–5.99	0
Continuous	1341	337	1.06	1.03–1.09	0	1750	578	1.07	1.04–1.09	0
All adenocarcinomas										
<25.0	614	222		Referent		705	352		Referent	
25.0–29.9	532	231	1.20	0.92–1.58	17	739	521	1.33	1.02–1.74	44
30.0–34.9	136	91	1.88	1.32–2.67	0	224	245	2.09	1.58–2.77	13
35.0–39.9	47	29	1.68	0.97–2.93	0	62	76	2.98	1.5–5.93	45
≥40	12	8	3.74 <sup>b</sup>	1.33–10.54	0	20	29	4.23	2.21–8.09	0
Continuous	1341	583	1.06	1.04–1.09	0	1750	1223	1.08	1.05–1.11	54

Results were adjusted for age (categorical: <50, 50–59, 60–69, ≥70 years), gender, pack-years of smoking (categorical: <15, 15 to <30, 30 to <45, ≥45), education (study-specific) and other study-specific adjustment variables (e.g. study centre, where applicable). Summary odds ratios and 95% confidence intervals were obtained from random-effects meta-analytic models. The four studies that had heartburn and reflux information available were included in these analyses.

<sup>a</sup>Only one of the four studies with heartburn and reflux data was able to contribute a study-specific odds ratio to this summary estimate.

<sup>b</sup>Only two of the four studies with heartburn and reflux data were able to contribute a study-specific odds ratio to this summary estimate.

that BMI is a risk factor for OA and OGJA, the predominant causal theory of which is that obesity increases abdominal pressure, which subsequently relaxes the lower oesophageal sphincter, exposing the lower oesophagus to gastric acid and increasing the risk of GERD.<sup>20,48,56–58</sup> In support of this hypothesis, the prevalence of GERD has been shown to increase with increasing levels of BMI.<sup>8,12</sup>

The large size of this analysis presented us the unique opportunity to investigate potential mechanisms of these associations. When stratified by history of GERD symptoms, we found no difference in the pattern of associations between BMI and these adenocarcinomas. In addition, adjustment for GERD symptoms (ever/never) did not attenuate the ORs for associations between BMI and OA/OGJA. These observations do not dispute the idea that a mechanical effect of BMI that increases the

propensity for GERD and thus the risk for cancer exists, as we did not adjust for severity or frequency of GERD symptoms. Moreover, we could not adjust for asymptomatic GERD, as ascertainment of such would obviously have required all individuals to have undergone ambulatory 24-h pH-metry. However, what it may suggest is that an indirect, possibly proinflammatory, carcinogenic pathway between BMI and OA risk may exist, in addition to the accepted mechanical pathway of oesophageal sphincter distortion, increased intra-gastric pressure and increased risk of hiatal hernia. Spline models stratified by GERD and gender provided further evidence for an indirect proinflammatory pathogenic mechanism of BMI on OA risk—in individuals without a history of GERD symptoms, increasing BMI was associated with OA risk in men but not women. This may suggest that when inflammatory routes of

**Table 4** Adjusted summary odds ratios and 95% confidence intervals for the association between body mass index and adenocarcinomas of the oesophagogastric junction stratified by gender

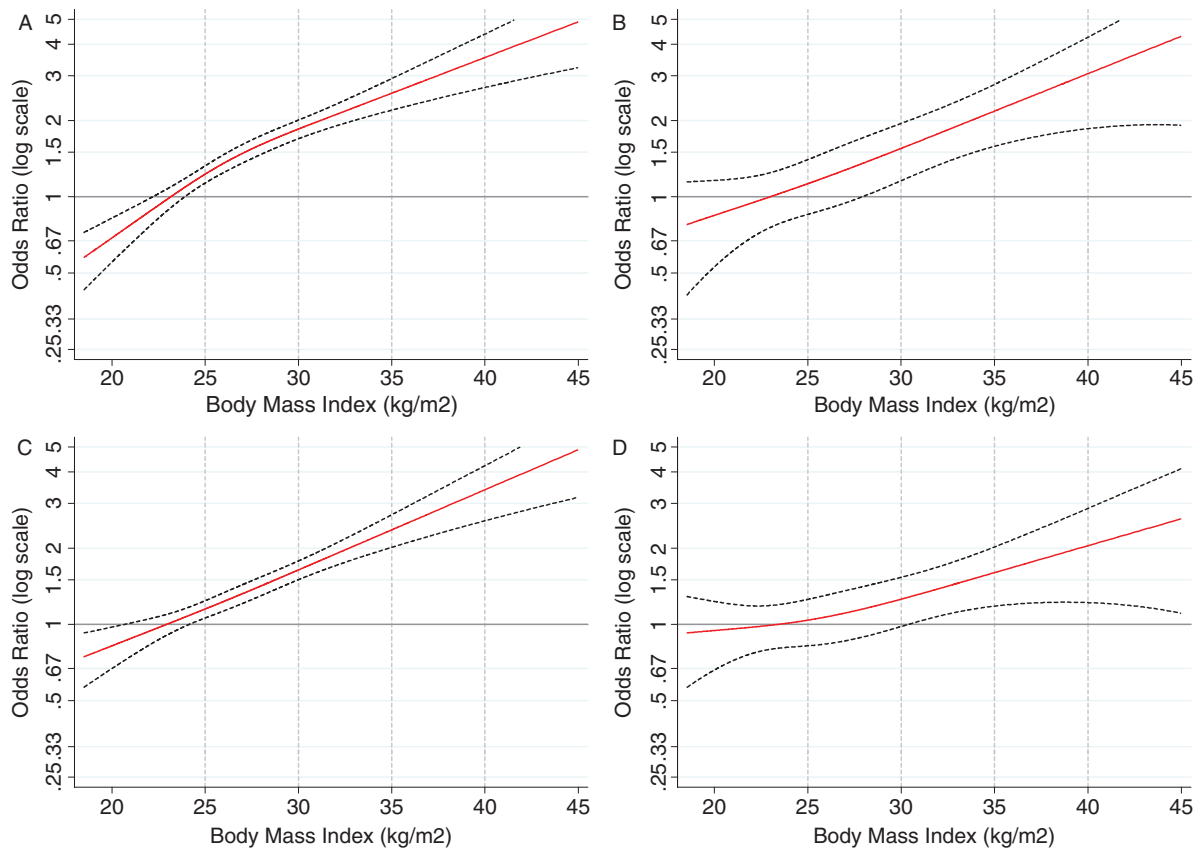
BMI (kg/m <sup>2</sup> )	OA					OGJA					All adenocarcinomas				
	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>	Controls (n)	Cases (n)	OR	95% CI	I <sup>2</sup>
<b>Males</b>															
<25.0	3171	477	Referent	Referent		3157	535	Referent	Referent		3171	1012	Referent	Referent	
25.0–29.9	3310	779	1.63	1.32–2.00	51	3274	675	1.36	1.19–1.55	0	3310	1454	1.49	1.29–1.71	38
30.0–34.9	743	280	2.47	1.94–3.13	26	733	268	2.24	1.85–2.71	0	743	548	2.38	1.95–2.91	32
35.0–39.9	150	69	2.87	1.89–4.36	17	149	68	2.50	1.78–3.53	0	150	137	2.58	1.94–3.43	2
≥40	33	22	4.47	2.42–8.26	0	33	16	3.16	1.63–6.11	0	35	38	3.49	2.09–5.84	0
Continuous	5588	1306	1.09	1.06–1.13	76	5525	1320	1.08	1.06–1.11	51	5588	2626	1.09	1.06–1.11	75
<b>Females</b>															
<25.0	1369	94	Referent	Referent		1529	128	Referent	Referent		1567	227	Referent	Referent	
25.0–29.9	794	80	1.24	0.67–2.29	56	873	67	1.04	0.67–1.61	26	910	147	1.06	0.81–1.38	0
30.0–34.9	331	49	2.66	1.59–4.46	17	296	36	1.71	1.06–2.77	0	362	85	1.74	1.24–2.43	0
35.0–39.9	110	11	1.38	0.57–3.35	0	114	15	1.80	0.92–3.52	0	115	29	1.83	1.06–3.15	0
≥40	46	13	5.88	2.28–15.1	0	51	9	3.08	1.25–7.56	0	57	23	3.55	1.87–6.75	0
Continuous	1522	228	1.07	1.04–1.10	13	1786	220	1.04	1.01–1.07	0	1878	457	1.05	1.03–1.07	0

Results were adjusted for age (categorical: <50, 50–59, 60–69, ≥70 years), pack-years of smoking (categorical: <15, 15 to <30, 30 to <45, ≥45), education (study-specific) and other study-specific adjustment variables (e.g. study centre, where applicable). Summary odds ratios and 95% confidence intervals were obtained from random-effects models.

I<sup>2</sup> estimates variability in results across studies.

OA = oesophageal adenocarcinoma; OGJA = oesophagogastric junction adenocarcinoma; BMI = body mass index; OR = odds ratio.





**Figure 1** Restricted cubic spline models of the relationship between body mass index and adenocarcinomas of the oesophagus and oesophagogastric junction. (a) Oesophageal adenocarcinoma in men. (b) Oesophageal adenocarcinoma in women. (c) Oesophagogastric junction adenocarcinoma in men. (d) Oesophagogastric junction adenocarcinoma in women. Plots are restricted to body mass indexes 18.5–45 and odds ratios 0.25–5 for clarity and consistency

associations are not saturated by the direct effects of GERD, the indirect effect can be detected. Such may be detectable in men, but not women, given the fact that android fat patterning, with highly metabolic visceral adipose tissue,<sup>20</sup> is common in men relative to the preferred gynoid fat patterning, with a much lower metabolic rate, of women.<sup>21,22</sup> Obesity-related hormones may induce oesophageal inflammatory damage, promoting proliferation and malignant transformation.<sup>24,59,60</sup> Although we lack central adiposity metrics to test the theory directly, the evidence we present is provocative. However, our findings do not preclude the possibility of collider-stratification bias<sup>61</sup> resulting from the more complex and possibly less direct relationships among obesity, GERD and OA/OGJA. This could occur if the relationship between GERD and BMI is mediated by a higher BMI giving way to increased severity and/or duration of GERD, in addition to the previously posited metabolic carcinogenic effects that a higher BMI may confer.<sup>8,12,14,20,24,30,57–66</sup> In addition, it should be noted that our findings contrast with those of at least four previous studies<sup>15,19,56,67</sup> that found stronger associations between BMI and OA/OGJA in individuals with a history of GERD symptoms, with the magnitude of the association increasing with

increasing duration and severity of symptoms.<sup>67</sup> However, these studies, some of which are included in the current analyses, suffered small sample sizes, raising the possibility that inconsistent findings could be attributed, at least in part, to unstable risk estimates. Lastly, and supporting the idea of direct mechanical (distortion of the lower oesophageal sphincter, increased intra-gastric pressure, increased risk of herniation) and indirect metabolic effects on OA risk, was the observation of synergism between BMI and GERD symptoms, with an excess risk attributable to synergistic interaction of 0.64 (0.12–1.17). Such interaction was previously suggested in a paper by Whiteman *et al* in an analysis of one of the studies included in this pooled analysis presented herein.<sup>19</sup> As a whole, the evidence we present advocates for at least two pathways through which increased BMI can modify OA risk, which may also be related to the large gender disparity of these malignancies,<sup>6</sup> given gender differences in adipose patterning. Although the stratified models suggest that the BMI–OA/OGJA relationships may vary by gender in some BMI categories, with stronger estimates observed in overweight and obese men, relative to equivalent estimates in women, it is important to keep in mind that, even in this large consortial analysis, the number of

**Table 5** Interaction statistics for departure from additivity

Variables tested for interaction with body mass index	Departure from additivity		
	ICR (95% CI) (null hypothesis = 0)	AP (95% CI) (null hypothesis = 0)	S (95%CI) (null hypothesis = 1)
OA vs controls			
Cigarette smoking	0.22 (−0.30, 0.73)	0.07 (−0.09, 0.22)	1.11 (0.87, 1.40)
Alcohol	0.05 (−0.30, 0.40)	0.04 (−0.25, 0.34)	1.31 (0.12, 13.74)
<i>H. pylori</i> (negative)	0.06 (−0.77, 0.89)	0.03 (−0.42, 0.49)	1.08 (0.37, 3.20)
Heartburn	0.44 (−0.16, 1.04)	0.18 (−0.04, 0.39)	1.42 (0.89, 2.26)
Reflux	0.14 (−0.31, 0.58)	0.08 (−0.16, 0.32)	1.20 (0.64, 2.28)
Heartburn or reflux <sup>a</sup>	<b>0.64 (0.12, 1.17)</b>	<b>0.20 (0.05, 0.35)</b>	<b>1.42 (1.04, 1.94)</b>
OGJA vs controls			
Cigarette smoking	0.25 (−0.28, 0.78)	0.08 (−0.08, 0.23)	1.12 (0.88, 1.44)
Alcohol	0.02 (−0.30, 0.33)	0.02 (−0.36, 0.40)	0.90 (0.16, 4.97)
<i>H. pylori</i> (negative)	−0.37 (−0.97, 0.22)	−0.44 (−1.18, 0.30)	
Heartburn	0.05 (−0.34, 0.45)	0.04 (−0.22, 0.29)	1.12 (0.48, 2.58)
Reflux	0.29 (−0.01, 0.58)	0.25 (0.00, 0.50)	
Heartburn or reflux	0.30 (−0.01, 0.60)	0.20 (0.00, 0.40)	2.51 (0.42, 14.98)

AP = attributable proportion due to interaction; ICR = interaction contrast ratio; OR = odds ratio; S = synergy index.

<sup>a</sup>The excess risk attributable to the synergistic interaction of heartburn or reflux and high BMI ICR, attributable proportion (AP) of OA.

women available for analysis was limited. These limitations are also applicable to a previous meta-analysis<sup>48</sup> and three other published studies<sup>68–70</sup> that have made similar observations of differences by gender.<sup>6,20–22</sup>

Several limitations of this study should be considered when interpreting our findings. First, none of the studies included in these analyses collected data on fat distribution, including body shape, and few collected waist circumference at different ages during adulthood. Consequently, fat distribution could not be evaluated in our analyses. Future studies should identify and use improved measures of central obesity and other measures of the body habitus, including those that could be retrospectively documented.<sup>21,71</sup> We have proposed that one of many ways this could be achieved is by retrospectively querying study participants about life-course changes in clothing sizes, particularly trouser waist size, at least for men, focusing on changes in adulthood.<sup>21</sup> Results from two of three studies that evaluated waist circumference and BMI in relation to OA<sup>19,26,72</sup> suggest that central obesity is a risk factor for OA, and a study of Barrett's oesophagus, an OA precursor, suggests visceral fat may influence risk independent of BMI.<sup>73</sup>

A second potential limitation of our study is that the study-specific analyses are not adjusted for dietary intake, primarily because of differing ways these data were collected across studies. However, strong associations between BMI and OA/OGJA have been reported, regardless of whether adjustments are made for dietary intake.<sup>15,74</sup>

A third limitation is that our pooled analysis predominantly consists of case-control studies that lack

the ability to determine the sequence of events between obesity and OA/OGJA, as BMI ascertainment among these studies was limited to  $\geq 1$  years before interview. However, restricting our analyses to individuals with a BMI  $>18.5$  did not alter our findings. Moreover, the association between BMI and OA/OGJA was also found in the two prospective cohort studies. Furthermore, such differential recall in case-control studies would attenuate the magnitude of the risk for the association between BMI and OA/OGJA, thus assuaging any concerns that our findings are due to underestimates of past body weight in patients. Also related to the timing of case ascertainment relative to cancer onset is the potential limitation that data for this pooled analysis include case accrual over a 25-year period (1964–2006), during which time there have been rapid increases in the prevalence of obesity in all countries from which the included studies derive. However, we found no evidence of effects by calendar period, by visual inspection of forest plots and meta-regression of mid-year of recruitment.

In summary, this consortial analysis of pooled individual participant data has provided evidence that increasing BMI is associated with an increasing risk of OA and OGJA, and that these relationships are similar in those with and without a history of GERD symptoms. In addition, we provide tentative evidence for effect modification by gender in those without GERD symptoms and, lastly, evidence of synergistic interactions between BMI and GERD. Future studies should focus on elucidating the mechanisms that underlie these observations, specifically the multifaceted effects of obesity on the risk of OA.

## Supplementary Data

Supplementary Data are available at *IJE* online.

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**Conflict of interest:** None declared.

### KEY MESSAGES

- BMI is directly associated with OA risk in both men and women and in those with and without GERD symptoms.
- Findings suggest an indirect proinflammatory route of association between BMI and OA exists, as well as direct mechanical effects of android fat.
- Effects of BMI and GERD symptoms on OA risk may be synergistic.

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