

# Role of body composition and metabolic profile in Barrett's oesophagus and progression to cancer

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**Background and aims** The aim of this study was to evaluate the risk for Barrett's oesophagus (BE) on the basis of body composition, metabolic pathways, adipokines and metabolic syndrome (MS), as well as their role in cancer progression.

**Methods** In patients with and without BE at gastroscopy, data on MS, BMI, waist/hip ratio for abdominal obesity (AO) and body fat percentage by bioimpedance were obtained. Fasting plasma glucose, insulin, HbA1c, lipid, serum adiponectin and leptin levels were measured. The homeostasis model assessment (HOMA-IR) was used to estimate insulin resistance. Histological findings for BE were correlated with the above parameters. Risk factors for BE identified using univariate analysis were entered into a multivariate logistic regression analysis.

**Results** A total of 250 patients and 224 controls (F/M: 189/285, mean age 58.08 ± 15.51 years) were enrolled. In the BE and control groups, 39.6 versus 31.3% were overweight, 32 versus 22.8% were obese, 75.6 versus 51.3% had AO, and 28.1 versus 18.9% were metabolically obese, respectively. AO [odds ratio (OR) 3.08], increased body fat percentage (OR 2.29), and higher BMI (overweight: OR 2.04; obese: OR 2.26) were significantly associated with BE. A positive trend was found in Normal Weight Obese Syndrome (OR 1.69). MS was associated with BE (overweight: OR 3.05; obese: OR 5.2; AO: OR 8.08). Insulin levels ( $P=0.05$ ) and HOMA-IR ( $P<0.001$ ) were higher in BE. AO was the only independent risk factor associated with BE (OR 1.65;  $P=0.02$ ) and high-grade dysplasia (OR 2.44) on multivariate analysis.

**Conclusion** AO was strongly associated with BE and dysplasia. BE was associated with MS and higher insulin/HOMA-IR, suggesting the activation of specific metabolic pathways in patients with altered body composition. *Eur J Gastroenterol Hepatol* 28:251–260

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## Introduction

Over the last few decades there has been a marked increase in the incidence of oesophageal adenocarcinoma (OAC) throughout North America and Europe at a rate exceeding that for any other solid tumour [1].

The underlying reasons for this are unclear, although gastro-oesophageal reflux, smoking and central adiposity are risk factors [2]. Oesophageal cancer is now the sixth most common cause of cancer-related death and accounts for around 5% of all cancer-related deaths in the UK [3]. Early diagnosis can substantially improve survival in

OAC. Barrett's oesophagus (BE) remains the strongest recognized risk factor for OAC and, therefore, surveillance endoscopic programmes have been endorsed to prevent cancer progression in patients with BE [3,4]. In clinical practice, the presence of dysplasia identifies patients with BE who require treatment [5,6].

In parallel to OAC, rates of obesity (defined as BMI > 30 kg/m<sup>2</sup>) and type 2 diabetes (T2D) have risen to epidemic proportions in the USA, Europe and Asia [7]. In the UK, in 2010, 26.1% of adults were reported to be obese, one of the highest rates in Europe, and 4.3% were estimated to have T2D [8]. Although other factors such as genetic predisposition may contribute to obesity, in general, increased caloric intake and decreased physical activity have been identified as primary causes for the observed trends [1,9]. Literature suggests that visceral abdominal fat is associated with an increased risk for T2D, ischaemic heart disease and malignancies including colorectal cancer [10,11].

Recent studies have clearly implicated chronic gastro-oesophageal reflux disease (GERD) and several lifestyle risk factors, including tobacco consumption, diet and particularly obesity, as being associated with increased risk for OAC, although the mechanism accounting for this link is unclear [12]. Reports describing how obesity *per se* predisposes individuals to GERD and BE through an increase in abdominal pressure have yielded conflicting results. A pathway from reflux to inflammation through metaplasia and dysplasia is the dominant hypothesis [13].

*European Journal of Gastroenterology & Hepatology* 2016, 28:251–260

**Keywords:** Barrett's oesophagus, oesophageal cancer, obesity

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**Received** 9 August 2015 **Accepted** 23 October 2015

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Abdominal fat is believed to play a crucial role in the development of oesophageal diseases, not only through the chronic increase in intra-abdominal pressure inducing oesophageal acid exposure but also through the endocrine function of the adipose mass, which represents an important source of proinflammatory cytokines (interleukin-1 $\beta$ , interleukin-6, tumour necrosis factor- $\alpha$ ), leading to increased levels of leptin and procoagulant factors and reduced levels of protective adipokines (i.e. adiponectin) [12–27].

BMI is a widely used measure of nutrition status and adiposity and is correlated with the risk for T2D and cardiovascular disease [28]. BMI, however, does not account for BF distribution. Central (visceral or abdominal) obesity, defined by the waist/hip ratio (WHR), is strongly correlated with insulin resistance and a greater risk for obesity-related morbidity compared with overall adiposity [29,30]. In particular, visceral obesity has been associated with oesophageal and junctional adenocarcinomas [31]. Recently, a new category of individuals with a higher risk of developing obesity-related diseases has been identified. Females with normal weight (BMI <25.0 kg/m<sup>2</sup>) but whose fat mass is greater than 30% of their total body weight, localized typically in the abdomen, are considered ‘metabolically’ obese and affected by ‘Normal Weight Obese Syndrome’ (NWOS) [32,33]. Recognizing and managing metabolically obese normal weight individuals is of major importance as they will benefit from preventive strategies.

Establishing an association between BE and obesity, body composition, metabolic syndrome (MS) and metabolic profile characteristics, along with further understanding of causality, would provide opportunities for intervention and prevention; this represents a crucial public health issue, given the growing obesity epidemic worldwide. The aim of our study was, therefore, to evaluate the association of obesity, body composition characteristics, dysfunction of metabolic indices/pathways and adipokines in patients with and without BE, and to examine their potential role in the metaplasia, dysplasia, cancer pathway in BE.

## Patients and methods

This was a prospective single-centre case/control study conducted at University College Hospital, London, UK (UCLH), where subjects were enrolled from May 2011 to May 2013. This research was approved by an independent ethics committee, East Central London REC 1. Funding was secured by application to the Clinical Research and Development Committee Research Funding from The UCLH Charities Fast Track Grant (Award number CDRC Reference: GCT/2011/MB). Patients were invited to participate in the study through letters when receiving their appointment for clinically indicated oesophagogastroduodenoscopy (OGD).

Patients with known BE were recruited sequentially from the Endoscopy Unit during the surveillance/therapeutic OGD programme for BE (Fig. 1).

The control group was also recruited sequentially from among patients booked to undergo an elective OGD for any other indication and from among those who did not have BE or OAC at endoscopy. If BE was newly diagnosed, patients were assigned to the case group.

The eligibility and exclusion criteria have been summarized in Table 1.

## Anthropometry, body composition analysis and metabolic screening

After the patients signed the informed consent form, details on demographics (age, sex and ethnicity), the presence of metabolic syndrome (hypertension, T2D and dyslipidaemia) and current medications were recorded. In addition, the required anthropometric measurements were taken: waist and hip circumferences, using flexible tape, and height and weight measurements, using a study-dedicated stadiometer (Seca 213; Seca, Birmingham, UK) and digital scale (Seca 813). Body composition was analysed through bioimpedance using QuadScan 4000 Bodystat (Bodystat Ltd, Douglas, Isle of Man, UK), a multifrequency bioelectrical impedance analysis unit.

## Venous blood sampling and metabolic pathways profile

A fasting (8 h) blood sample (~15 ml in two heparinized tubes) was taken for analysis. Initial parameters analysed in the UCLH laboratory included plasma glucose, total cholesterol and triglyceride, high-density lipoprotein, insulin and HbA1c. A second heparinized blood sample tube was taken to the Clinical Research Facility at UCLH to be spun down to separate plasma from serum, which was then stored in a –80°C freezer. Subsequently, these samples were analysed in the Laboratory of the Centre for Obesity Research using Millipore ELISA kits (Human Leptin ‘Dual Range’ ELISA and Human Adiponectin Elisa Kit; Millipore, Feltham, UK) to determine serum leptin and adiponectin levels. Each kit is sufficient to run one 96-well plate, measuring 38 samples in duplicate.

## Patient classification

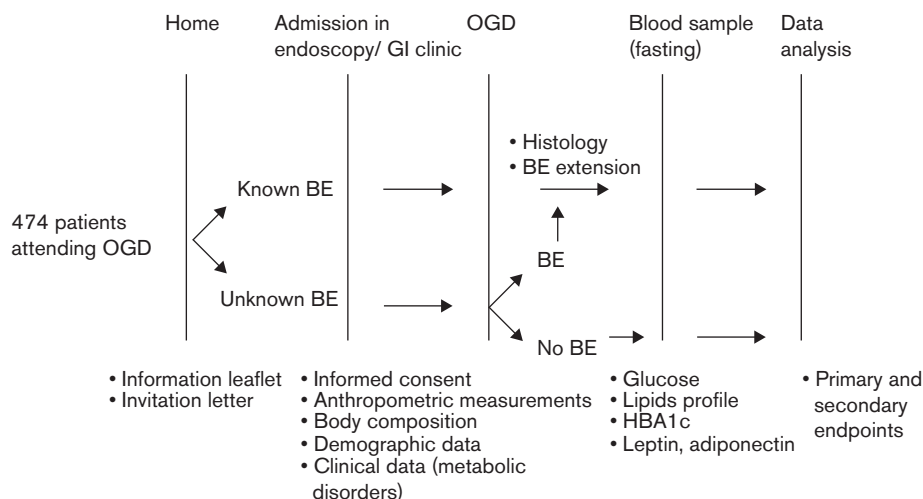
Patients were classified according to BMI, abdominal obesity (AO by WHR) and NWOS in women [32]. A BMI greater than 30 kg/m<sup>2</sup>, and a WHR greater than 90 cm in men and greater than 85 cm in women were defined as obese or abdominal (visceral) obesity (AO), respectively [34]. NWOS was defined as females with normal BMI but a total BF% greater than 30% [34–36]. The presence of MS was assessed using International Diabetes Federation criteria [37].

Insulin resistance (IR) was estimated on the basis of the homoeostasis model assessment (HOMA), using the following formula: HOMA-IR = FPI  $\times$  FPG/405, where FPI is the fasting plasma insulin concentration ( $\mu$ U/ml) and FPG is fasting plasma glucose (mg/dl) [38]. Table 2 provides the definitions used to classify patients based on MS, BMI and body composition.

## Endoscopy

BE was defined according to British Society of Gastroenterology guidelines [39].

During OGD, BE was classified on the basis of the Prague C and M Endoscopic Criteria, and biopsies were taken for histopathological reporting, in keeping with standard clinical practice for BE [40]. Endoscopic treatment was performed as clinically indicated. This also applied to any individual in the control group who was found to have BE. A definitive diagnosis of BE was



**Fig. 1.** Study design. BE, Barrett's oesophagus; OGD, oesophagogastroduodenoscopy.

**Table 1.** Study inclusion and exclusion criteria

Inclusion criteria <sup>a</sup>	Exclusion criteria
Age 18–79 years	Weight loss > 10% in the last 12 months
Enrolled in Barrett's oesophagus endoscopic surveillance/therapeutic programme at UCLH	Decompensated liver disease
Scheduled for OGD (indication unrelated to Barrett's oesophagus)	Inflammatory bowel disease
	Coeliac disease
	Previous upper gastrointestinal tract surgery
	Known malignancy or undergoing treatment for previously resected malignancy
	Inability to provide informed consent

OGD, oesophagogastroduodenoscopy; UCLH, University College Hospital, London, UK.

<sup>a</sup>Long term therapies for concomitant disease were allowed.

**Table 2.** Definitions used to classify patients

Definition	Criteria
Obesity	BMI > 30 kg/m <sup>2</sup>
Overweight	BMI 25–30 kg/m <sup>2</sup>
Normal weight	BMI 18.5 to < 25 kg/m <sup>2</sup>
Abdominal obesity	WHR > 0.85 in female individuals; WHR > 0.90 in male individuals
Metabolic Syndrome	Abdominal obesity plus any of the following: blood pressure ≥ 130/85 mmHg, or receiving treatment;
Defined by International Diabetes Federation criteria	triglyceride ≥ 1.7 mmol/l, or receiving treatment; HDL cholesterol < 1.03 mmol/l ♂ / < 1.29 mmol/l ♀, or receiving treatment; fasting glucose TG ≥ 1.7 mmol/l, or receiving treatment; or previous diagnosis of type 2 diabetes
Insulin resistance	Fasting plasma insulin × fasting plasma glucose/405
Defined by HOMA-IR	
Normal Weight Obese Syndrome in female individuals	Body fat % > 30% and BMI 18.5–25 kg/m <sup>2</sup>

HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment-insulin resistance; TG, triglyceride; WHR, waist/hip ratio.

confirmed only after histopathological examination of the biopsy. Long-segment BE was defined as 3 cm or greater, whereas short-segment BE was defined as less than 3 cm.

Histopathological and Prague classification of BEs were based on the highest dysplasia or cancer score and the maximum length, at any stage of treatment/surveillance. All biopsies demonstrating dysplasia were reviewed by two expert pathologists.

### Statistics

The sample size was calculated to show the difference in the proportion of participants who were obese, overweight or metabolically obese in the BE group compared with the control group.

The prevalence of BE in visceral obese patients is around 40%, as previously reported, whereas the prevalence of BE is 1.6% in population-based analysis and 10% in patients with symptoms [41–43]. It is known that, in England, the proportion of men classified as obese increased from 13.2% in 1993 to 23.1% in 2005, and from 16.4 to 24.8% among women during the same period. It is known that the risk of being overweight or obese increases with age. About 28% of men and 27% of women aged between 16 and 24 years are overweight or obese, whereas 76% of men and 68% of women aged between 55 and 64 years are overweight or obese [44,45]. In the USA, the prevalence of AO is 27.1, 20.2 and 21.4% in White, Black and Hispanic men, respectively.

The corresponding values among women are 43.2, 56.0 and 55.4% [46]. Another study in Europe shows that the prevalence of AO is higher in women than in men (30.6 vs. 23.9%) and increases with age [47]. Stein and El-Serag demonstrated a 15% difference between BE and controls in the proportion of patients who were overweight or obese [48]. There are no data available on the prevalence of 'metabolic' (normal weight) obesity in the general population.

On the basis of the current available data summarized above, we assumed that ~55% of the normal group would have been overweight, obese, abdominally obese or metabolically obese. A difference of 15% between the patients and controls was chosen as clinically relevant. With a 5% significance level and 90% power, at least 230 participants were required in each group.

The  $\chi^2$ -test, Fisher's test, Student's *t*-test and logistic analysis were used for comparison. The identified risk factors significantly associated with BE at univariate analysis were subsequently entered into a multivariate logistic regression analysis.

## Results

### Demographics

A total of 474 patients were enrolled, among whom 189 were female (F) and 285 were male (M); the mean age was  $58.08 \pm 15.51$  years. Among the 250 patients with BE, only 57 (22.8%) were female, and the mean age of the BE patients was higher than that of controls ( $63.7 \pm 12.3$  vs.  $52.03 \pm 16.44$  years; data summarized in Table 3).

Overall, 97.2% of patients and 77.2% of controls enrolled were White. BE cases were mainly tertiary referrals from a large catchment area, whereas most controls were referred locally from North London. On the basis of demographic characteristics, age (cutoff: 57 years) and male sex [M/F 193/57; odds ratio (OR) 5.01,  $P < 0.0001$ ] were identified as risk factors for BE.

### Body composition

In the BE group, 99 patients (39.6%) were overweight, 80 (32%) were obese, 189 (75.6%) had AO, and, among female individuals, 16 (28.1%) were classified as NWOS. In the control group, 70 patients (31.3%) were overweight, 51 (22.8%) were obese, 115 (51.3%) had AO, and, among the female individuals, 18.9% were classified as NWOS (data summarized in Table 3).

When analysing the data by BMI scale for obesity, 22.8% of BE cases had a BMI between 30 and 35 and 9.2% had BMI greater than 35 (morbidly obesity). In total, 71.6% of the cases were either overweight, obese, AO or female individuals with NWOS, compared with 53.5% in the control group, confirming our initial hypothesis of a difference greater than 15% between patients and controls (18.1%).

Increased BF% (F > 30% and M > 25%) *per se* was present in 198 (79.2%) BE patients versus 143 (63.8%) controls.

Comparison of anthropometric characteristics and body composition showed that AO (OR 3.08,  $P < 0.0001$ ), increased BF% (OR 2.29;  $P = 0.0002$ ) and higher BMI (overweight OR 2.04;  $P < 0.001$ ; obese OR 2.26;

$P = 0.0006$ ) were significantly associated with BE. Our data demonstrated a positive trend for NWOS (OR 1.69;  $P = 0.1$ ); the nonsignificance is likely because of the small number of female patients (57 patients vs. 132 controls).

When adjusted by sex, age and race into a multivariate analysis, the only independent risk factor associated with BE was AO (OR 1.65;  $P = 0.02$ ).

### Metabolic risk

Among the patients and controls, 96 and 39 (38.4 vs. 17.4%, OR = 3.00,  $P < 0.00001$ ) were affected by MS, respectively. Specifically, MS was present in 39.7 versus 34.2% (OR 3.05,  $P < 0.001$ ), 43.7 versus 21.9% (OR 5.2,  $P < 0.001$ ), 92.1 versus 54.9% (OR 8.08,  $P < 0.0001$ ) of overweight, obese, and AO patients with BE versus controls, respectively (data summarized in Table 3).

History of hypertension (37.4 vs. 21.9, OR 2.3,  $P < 0.0001$ ) and dyslipidaemia (72.8 vs. 55.4, OR 2.15,  $P = 0.0001$ ) were significantly correlated with BE, whereas T2D and glucose intolerance (29.2 vs. 21.4, OR 1.51,  $P = 0.05$ ), but not T2D alone, were also identified as risk factors (19.6 vs. 16.1, OR 1.22,  $P = \text{NS}$ ). HbA1c was not significantly associated with BE, possibly because of the use of antidiabetic drugs in this group.

Insulin levels ( $10.2$  vs.  $7.1$   $\mu\text{IU/ml}$ ,  $P = 0.05$ ) and HOMA-IR ( $2.54 \pm 2.66$  vs.  $1.78 \pm 1.82$ ,  $P < 0.001$ ) were higher in BE cases compared with controls.

A trend was observed towards decreased adiponectin levels in BE cases versus controls, whereas leptin showed no correlation. When the analysis was carried out by categories for adiponectin (F < 11.9, 11.9–18.6 and  $\geq 18.7$ , and M < 7.1, 7.1–11.3 and  $\geq 11.4$   $\mu\text{g/ml}$ ), the trend remained, but was not significant.

### Intestinal metaplasia, dysplasia, cancer pathway

The association between anthropometric/body composition characteristics and changes in metabolic pathways with the metaplasia/dysplasia pathway was analysed in the BE group (data summarized in Table 4).

Intestinal metaplasia alone and intestinal metaplasia with dysplasia were present in 57.2 and 42.8% of cases, respectively. In particular, dysplasia was present in 47% of patients with AO, 51% with MS and 58.9% with T2D. In contrast, only 28.1% of patients without AO, 37.3% with MS and 36.2% with T2D had BE that progressed to dysplasia.

When analysing low-grade and high-grade dysplasia (LGD and HGD) separately, AO was the only metabolic parameter independently correlated with HGD alone (37.5 vs. 21%, OR 2.44,  $P = 0.01$ ).

Insulin levels and HOMA-IR were progressively higher in metaplasia, low-grade dysplasia and HGD (6, 9.55 and 11.6 SCALE, respectively, for insulin levels and 2.28, 2.51 and 3 for HOMA-IR).

BMI, dyslipidaemia, BF% and hypertension were not associated with progression to cancer, and length of BE was not significantly associated with any parameter of body composition and metabolic dysfunction analysed.

**Table 3.** Demographics, body composition, metabolic risks and clinical characteristics in cases and controls

	Barrett's oesophagus		Univariate analysis		Multivariate analysis	
	No (n=224)	Yes (n=250)	OR (95% CI)	P	OR (95% CI)	P
Age (mean±SD) (years)	52.03±16.44	63.74±12.37	1.05 (1.04–1.07)	<0.0001		
Sex [n (%)]						
Female (F)	132 (58.9)	57 (22.8)		NS		
Male (M)	92 (41.1)	193 (77.2)	4.85 (3.26–7.20)	<0.0001		
Ethnicity						
White	173 (77.2)	243 (97.2)		NS		
Black	21 (9.4)	1 (0.4)	0.03 (0.01–0.25)	NS		
Asian	26 (11.6)	5 (2.0)	0.14 (0.05–0.36)	NS		
NA	4	1	–			
Hypertension						
No	175 (78.1)	151 (62.6)				
Yes	49 (21.9)	99 (37.4)	2.34(1.56–3.51)	<0.0001		
Diabetes						
No	188 (83.9)	201 (80.4)				
Yes	36 (16.1)	49 (19.6)	1.22 (0.76–1.97)	NS		
Diabetes/glucose intolerance						
No	176 (78.6)	177 (70.8)				
Yes	48 (21.4)	73 (29.2)	1.51 (0.99–2.30)	0.05		
Hyperlipidaemia						
No	100 (44.6)	68 (27.2)				
Yes	124 (55.4)	182 (72.8)	2.15 (1.47–3.17)	0.0001		
Abdominal obesity						
No	107 (47.8)	57 (22.8)				
Yes	115 (51.3)	189 (75.6)	3.08 (2.07–4.59)	<0.0001	1.65 (1.07–2.56)	0.02
NA	2	4	–			
Metabolic syndrome						
No	183 (81.7)	150 (60.0)				
Yes	39 (17.4)	96 (38.4)	3.00 (1.96–4.62)	<0.0001		
NA	2	4	–			
BMI						
Normal	101 (45.1)	70 (28.0)				
Overweight	70 (31.3)	99 (39.6)	2.04 (1.32–3.14)	0.0012		
Obesity	51 (22.8)	80 (32.0)	2.26 (1.42–3.60)	0.0006		
NA	2	1	–			
BMI for obese patients						
30–35	35 (15.6)	57 (22.8)	2.34 (1.40–3.95)	0.0013		
>35	16 (7.1)	23 (9.2)	2.07 (1.02–4.20)	0.04		
NA	2	1	–			
Body fat (BF) %						
M < 30, F < 25%	73 (32.6)	44 (17.6)				
M > 30, F > 25%	143 (63.8)	198 (79.2)	2.29 (1.49–3.53)	0.0002		
NA	8	8				
NWO syndrome						
Female, normal BMI, BF > 30% (n=189)						
No	106 (80.3)	40 (70.2)				
Yes	25 (18.9)	16 (28.1)	1.69 (0.82–3.50)	NS		
NA	1	1	–			
Reflux symptoms						
No	131 (58.5)	84 (33.6)				
Yes	93 (41.5)	166 (66.4)	2.78 (1.91–4.04)	<0.0001		
Hiatus hernia						
No	179 (79.9)	109 (43.6)				
Yes	45 (20.1)	141 (56.4)	5.14 (3.40–7.76)	<0.0001		

CI, confidence interval; NA, not applicable (data not collected); NS, not significant; NOW, Normal Weight Obese; OR, odds ratio.

### Correlation with reflux symptoms, hiatus hernia and reflux oesophagitis

The choice of the control group was driven by the final aim to ensure identification of individuals metabolically at risk of developing BE compared with the general population, even if experiencing reflux symptoms or having a diagnosis of hiatus hernia and reflux oesophagitis. To validate our hypothesis further, we carried out a subanalysis dividing patients into BE versus reflux oesophagitis cases (controls: 28 patients). The presence of reflux symptoms and hiatus hernia was significantly higher in the BE group compared with controls (66.4 vs. 25%,  $P=0.001$  and 56.4 vs. 32.1%,  $P=0.002$ , respectively). Interestingly, MS, obesity

defined by BMI, hypertension and T2D/glucose intolerance were associated with BE compared with reflux oesophagitis (38.4 vs. 14.3%,  $P=0.01$ ; 32 vs. 14.3%,  $P=0.06$ ; 37.4 vs. 10.7%,  $P=0.001$ ; 29.2 vs. 10.7%,  $P=0.04$ , respectively; data summarized in Table 5).

### Is Barrett's oesophagus part of the spectrum of metabolic syndrome?

We postulated that BE might represent a component of the disease spectrum of MS. If BE was included as one of the criteria to define MS, then 44% of the total enrolled BE patients in our study would be considered as affected by MS versus 28.5% on the basis of the current definition of

**Table 4.** Metabolic risk for cancer pathway and correlation with extension of Barrett's oesophagus

Histology/extension	Barrett's oesophagus patients			Univariate analysis	
				OR (95% CI)	P
	Abdominal obesity				
	No (n = 57) [n (%)]	Yes (n = 189) [n (%)]			
Metaplasia	41 (71.9)	100 (52.91)		1.8 (0.57–5.66) 2.44 (1.2–4.9)	0.01
LGD	4 (7.0)	18 (9.52)			
HGD	12 (21.1)	71 (37.57)			
Short Barrett	21 (36.8)	65 (34.4)			
Long Barrett	36 (63.2)	124 (65.6)			
	Metabolic syndrome				
	No (n = 150) [n (%)]	Yes (n = 96) [n (%)]			
Metaplasia	94 (62.7)	47 (48.96)			
LGD	14 (9.3)	8 (8.33)			
HGD	42 (28.0)	41 (42.71)			
Short Barrett	53 (35.3)	33 (34.4)			
Long Barrett	97 (64.7)	63 (65.6)			
	NWO syndrome				
	No (n = 40) [n (%)]	Yes (n = 16) [n (%)]			
Metaplasia	30 (75.0)	8 (50.00)			
LGD	0 (0.0)	2 (12.50)			
HGD	10 (25.0)	6 (37.50)			
Short Barrett	19 (47.5)	9 (56.3)			
Long Barrett	21 (52.5)	7 (43.8)			
	BMI				
	Normal (n = 70) [n (%)]	Overweight (n = 99) [n (%)]	Obese (n = 80) [n (%)]		
Metaplasia	42 (60.0)	61 (61.62)	40 (50.00)		
LGD	8 (11.4)	5 (5.05)	9 (11.25)		
HGD	20 (28.6)	33 (33.33)	31 (38.75)		
Short Barrett	24 (34.3)	36 (36.4)	27 (33.8)		
Long Barrett	46 (65.7)	63 (63.6)	53 (66.3)		
	Diabetes/glucose intolerance				
	No (n = 177) [n (%)]	Yes (n = 73) [n (%)]			
Metaplasia	113 (63.8)	30 (41.10)		0.002	
LGD	15 (8.5)	7 (9.59)			
HGD	49 (27.7)	36 (49.32)			
Short Barrett	65 (36.7)	22 (30.1)			
Long Barrett	112 (63.3)	51 (69.9)			
	Diabetes				
	No (n = 201) [n (%)]	Yes (n = 49) [n (%)]			
Metaplasia	122 (60.7)	21 (42.86)			
LGD	17 (8.5)	5 (10.20)			
HGD	62 (30.8)	23 (46.94)			
Short Barrett	76 (37.8)	11 (22.45)			
Long Barrett	125 (62.2)	38 (77.55)			
	Hypertension				
	No (n = 151) [n (%)]	Yes (n = 99) [n (%)]			
Metaplasia	90 (59.6)	53 (53.54)			
LGD	14 (9.3)	8 (8.08)			
HGD	47 (31.1)	38 (38.38)			
Short Barrett	49 (32.5)	38 (38.4)			
Long Barrett	102 (67.5)	61 (61.6)			
	Hyperlipidaemia				
	No (n = 68) [n (%)]	Yes (n = 182) [n (%)]			
Metaplasia	44 (64.7)	99 (54.40)			
LGD	8 (11.8)	14 (7.69)			
HGD	16 (23.5)	69 (37.91)			
Short Barrett	25 (36.8)	62 (34.1)			
Long Barrett	43 (63.2)	120 (65.9)			

HGD, high-grade dysplasia; LGD, low-grade dysplasia; NWO, Normal Weight Obese.

MS, allowing an additional 15.5% of individuals at risk of developing OAC to be identified.

We recognize that this speculation requires further studies and validation; however, it might potentially have a crucial role in the prevention of oesophageal cancer.

## Discussion

We have demonstrated that body composition and the insulin metabolic pathway, rather than obesity *per se*, have a direct role in the development of BE and progression to cancer. MS, obesity, hypertension and T2D/glucose

intolerance were associated with BE compared with reflux oesophagitis. Furthermore, we found that AO was strongly associated with HGD, in addition to BE. Finally, we demonstrated that BE was associated with MS, dyslipidaemia, T2D/glucose intolerance and hypertension.

Obesity represents a growing and challenging global health problem. Adult obesity rates have nearly quadrupled over the last 25 years, and two-thirds of UK adults are now overweight [44,45]. The number of obese children has increased by 47% between 1980 and 2013 [49].

**Table 5.** Correlation with reflux symptoms, hiatus hernia and reflux oesophagitis

	Barrett's oesophagus [n (%)]	Reflux oesophagitis [n (%)]	P-value
Total patients (n)	250	28	
Reflux symptoms	166 (66.4)	7 (25.0)	0.001
Hiatus hernia	143 (56.4)	9 (32.1)	0.002
Normal weight	70 (28)	13 (46.4)	NS
Overweight	99 (39.6)	11 (39.3)	NS
Obesity	80 (32.0)	4 (14.3)	0.006
AO	189 (75.6)	18 (64.3)	NS
MS	96 (38.4)	4 (14.3)	0.01
T2DM + IGT	73 (29.2)	3 (10.7)	0.04
Hypertension	99 (37.4)	3 (10.7)	0.001
Dyslipidaemia	182 (72.8)	16 (57.1)	NS

AO, abdominal obesity; IGT, glucose intolerance; MS, metabolic syndrome; NS, not significant; T2DM, type 2 diabetes.

Obesity contributes to up to one-third of the cancers of the colon, breast, kidney and stomach and has also been associated with OAC [10,11]. It is a risk factor for T2D, heart disease, stroke, osteoarthritis, high blood pressure, gallstones, infertility and depression and can reduce life-span by as much as 9 years [50]. Recently, it has become apparent that normal weight individuals with increased adiposity, particularly visceral fat, even in the absence of morbid obesity, are predisposed to developing MS and perhaps other obesity-related diseases, and they are considered metabolically obese [32,33].

High prevalence of MS and central adiposity in BE has been reported previously [18]. As BE is the strongest risk factor for OAC, establishing a causative link is an important public health issue because of their present epidemic proportions, to endorse preventive strategies. However, a direct causal link between obesity and OAC has not been conclusively established. In part, this could be explained by the use of BMI to stratify patients in previous studies rather than body composition or fat distribution as indicators of risk for obesity-associated diseases. BMI is in fact a crude parameter that does not take into consideration distribution of fat and related metabolic implications [51,52]. Nevertheless, a meta-analysis conducted by Kamat *et al.* [51] reported that increased BMI is associated with an increased likelihood of BE. When using waist circumference or WHR as a measure of adiposity distribution, the results were in favour of an association with BE but not in all studies [24,43,53]. These inconsistent data are likely due to tape-measured abdominal fat representing both visceral and subcutaneous components; although both exert a mechanical effect, only visceral fat secretes adipokines and is associated with insulin resistance. El-Serag *et al.* [54] evaluated the distribution of abdominal fat components on the basis of CT scanning, demonstrating that the surface area of visceral abdominal fat was significantly greater in patients with BE. In a meta-analysis, the same scientific group confirmed that oesophageal inflammation, metaplasia and neoplasia are associated with central adiposity, independent of BMI [55].

A univariate analysis of the risk factors for BE, conducted as part of our study, demonstrated that AO, increased BF%, higher BMI, MS, age (>57 years) and male sex were significantly associated with BE. A positive trend was demonstrated only in female individuals with NWOS.

More BE patients than controls were affected by hypertension and dyslipidaemia, demonstrating that BE is associated with MS. On multivariate analysis, the only independent risk factor for BE was AO, which, interestingly, is the only mandatory criterion that must be satisfied to define MS [36].

AO, MS and T2D were significantly associated with dysplasia, but only AO was correlated with HGD, suggesting a potential role of AO in the progression to cancer.

Ryan *et al.* [18] found that individuals with long-segment BE were significantly more obese and had higher fasting insulin levels than those with short-segment BE, suggesting that obesity might have a role in the extent of BE. Conversely, in our study, the length of BE was not significantly associated with body fat distribution.

The aetiology of the association between BE and obesity is under debate. It is known that an increased level of insulin promotes carcinogenesis through its proliferative and antiapoptotic actions and effects on the insulin growth factor family [56–59]. In a case-control study, increased levels of insulin and insulin-like growth factor-1 were found to be associated with BE, supporting the hypothesis that higher levels of these growth factors contribute to obesity-related carcinogenesis [60]. In our study, both insulin levels and HOMA-IR were significantly altered in BE, suggesting that the insulin metabolic pathway is involved in oesophageal carcinogenesis.

There is extensive but not conclusive literature on the relationship between adipokines and cancer. Adiponectin is a peptide secreted by adipocytes, and its plasma levels are inversely associated with obesity. Leptin is synthesized in adipocytes as a 16 kDa molecule, and its circulating level is directly proportional to the total amount of fat in the body. Current data show that a high serum leptin level is associated with an increased risk for BE in men but not women, and a high level of low molecular weight adiponectin is associated with a decreased risk for BE [16,32]. Mokrowieka *et al.* [61] did not find significantly higher leptin levels in BE, but they did find lower adiponectin levels in BE compared with GERD patients and controls. Deregulated leptin and adiponectin receptor expression present in obese individuals have been correlated with OAC, suggesting that pathways involving adipocytokines affect tumour biology [62].

Garofalo and Surmacz [63] examined the link between leptin and a variety of cancers including breast, colorectal, prostate, ovarian, endometrial and lung cancer, showing an association with cancer progression. Kelesidis *et al.* [64] published a review on the association between adiponectin and cancers including acute myelogenous leukaemia, and breast, colorectal, prostate, endometrial and gastric cancers, with evidence indicating an increased cancer risk.

In our study, a trend towards decreased adiponectin levels in BE compared with controls was observed, whereas leptin showed no correlation. However, the three multimeric circulating forms of adiponectin (low molecular weight, middle molecular weight and high molecular weight) were not analysed, and previous data have shown an association only between high levels of the low molecular weight form and decreased risk for BE, which might explain the lack of correlation in our results [61,65].

The present study has some limitations. Our results cannot be extended to different ethnicities, as the study

population included mainly Whites and it is likely that racial differences exist. Moreover, it is not possible to establish a temporal cause–effect link in terms of time of onset between the analysed risk factors and BE. In addition, smoking and diet habits were not included in our analysis: including those risk factors, however, would have only added an imprecise estimate of their effects on our relatively small sample size. The small number of female individuals in the case group meant that this subgroup was underpowered to demonstrate a definitive association between BE and NWOs, although a trend was apparent. Individuals with reflux symptoms, hiatus hernia and reflux oesophagitis were included in the control group, as it would not be economically sustainable or scientifically justified to propose screening of all individuals in the general population suffering from the above. In support of this, previous case–control studies found that WHR is associated with an increased risk for BE, independent of BMI and GERD symptoms [24,43]. Finally, we measured leptin and adiponectin levels in our patients but not other cytokines, although it is well known that visceral fat is responsible for the release of many other cytokines, such as interleukin-1 $\beta$ , interleukin-6 and tumour necrosis factor- $\alpha$ . It is important to recognize that the BE patients had a disproportionately high prevalence of dysplasia, given that all were recruited from a tertiary referral centre. We have shown that AO, MS and T2D were more common in the dysplasia group when compared with the nondysplastic BE group and, therefore, it is acknowledged that all the measured parameters are likely to be enlarged in this cohort of BE patients when compared with controls.

Our control group included patients with reflux oesophagitis and hiatus hernia. To identify which metabolic risk factors were still associated with BE, we carried out a subgroup analysis of this cohort. Interestingly MS, obesity defined by BMI, hypertension and T2D/glucose intolerance were associated with BE compared with reflux oesophagitis.

The association of BE with insulin resistance, MS, dyslipidaemia and hypertension suggests the activation of specific metabolic pathways in patients with altered BF distribution or BMI. The intestinal metaplasia, dysplasia, cancer pathway appears to be modulated by changes in the metabolic pathway, in particular in MS involving a carcinogenic insulin pathway. Additional research and validation of BE risk factors and the association between BE and MS are warranted to identify metabolically predisposed individuals in the general population who will benefit from early screening for BE, independently of the presence of reflux symptoms, to prevent OAC. Patients with GERD are more likely to be investigated endoscopically and eventually enter into a surveillance programme if BE is diagnosed. Obese individuals who do not develop GERD, often hidden because of the use of a proton-pump inhibitor, will not benefit from screening. Our study aimed to identify individuals at risk for BE on the basis of metabolic characteristics rather than presence of GERD.

Our study was designed to examine the risk of developing BE on the basis of body composition, obesity and metabolic pathway profile to identify risk factors in individuals who might benefit from a screening programme for OAC. The study, therefore, emphasizes the importance of health promotion programmes to prevent obesity and

metabolically related diseases. The possibility that modifying behavioural risk factors for BE might be an effective method of preventing the development of OAC should be explored. Abdominal obesity is a strong modifiable behavioural risk factor for BE.

### Acknowledgements

Authors' contributions: conception and design: Simona Di Caro, Matthew Banks. Analysis and interpretation of the data: Simona Di Caro, Lucia Fini, Matthew Banks. Collection and assembly of the data: Simona Di Caro, Margaret G Keane, Matthew Banks, Wui Hang Cheung, Laurence Lovat, Rehan Haidry, Laura Di Renzo, Antonino De Lorenzo. Drafting of the article: Simona Di Caro. Critical revision: Matthew Banks, Belinda Theis, Rachel L Batterham, Margaret G Keane. Final approval: Simona Di Caro, Wui Hang Cheung, Lucia Fini, Margaret G Keane, Belinda Theis, Rehan Haidry, Laura Di Renzo, Antonino De Lorenzo, Laurence Lovat, Rachel L Batterham, Matthew Banks.

Funding was provided by the Clinical Research and Development Committee Research Funding from The UCLH Charities Fast Track Grant (Award number CDRC Reference: GCT/2011/MB).

### Conflicts of interest

There are no conflicts of interest.

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