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Multifaceted association of overweight and metabolically unhealthy with the risk of Barrett's esophagus in the UK Biobank cohort

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The association of overweight/obesity and metabolically unhealthy (MU) with the risk of developing Barrett's esophagus (BE) remains uncertain. We evaluated whether MU and overweight/obesity are associated with increased BE incidence and whether they have a synergistic impact on BE development. We analyzed the body mass index (BMI) and metabolic indicators at baseline of 402,510 individuals from the UK Biobank with no history of BE. Overweight/obesity and MU were defined as BMI ≥ 25.0 kg/m^2 and presence of ≥ 1 MU indicators, respectively. Accordingly, the participants were categorized into four groups: (1) metabolically healthy non-overweight/obesity (MHNO), (2) metabolically unhealthy non-overweight/obesity (MUNO), (3) metabolically healthy overweight/obesity (MHO), and (4) metabolically unhealthy overweight/obesity (MUO). During a median follow-up of 13.5 years, 6195 (1.5%) individuals were newly diagnosed with BE. Among them, 39,281 (9.8%), 92,000 (22.9%), 25,297 (6.3%), and 245,932 (61.1%) individuals were classified as MHNO, MUNO, MHO, and MUO, respectively. In Cox regression analyses, both MU and overweight/obesity were independently associated with BE incidence. Moreover, BE incidence was significantly higher in the MUNO, MHO, and MUO groups, compared to the MHNO group. MU and overweight/obesity are independent risk factors for BE and have a synergistic effect on BE development.

Keywords Barrett's esophagus, Metabolically unhealthy, Overweight/obesity

Barrett's esophagus (BE) is a chronic condition that is characterized by the replacement of the normal squamous epithelial lining of the lower esophagus with specialized columnar epithelium containing goblet cells[1]. This metaplastic change is considered a precursor of esophageal adenocarcinoma (EAC). The incidence of EAC in patients with BE is much higher than that in the general population[2,3]. Studies on time trends have demonstrated that the prevalence of BE and incidence of EAC are increasing[3,4]. The pathogenesis of BE remains poorly understood but is thought to involve a complex interplay of genetic, environmental, and lifestyle factors. Gastroesophageal reflux disease (GERD), central obesity, advanced age, male sex, tobacco use, and Caucasian race are well-known risk factors for BE development[5–8]. Because patients with BE have a high risk of developing EAC, timely identification and vigilant monitoring of BE are important for preempting the onset of EAC and ensuring a favorable prognosis. Hence, a thorough analysis of the risk factors linked to the onset of BE is imperative to advance our understanding of its pathogenesis, as well as to formulate precise prevention and intervention strategies.

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Overweight/obesity is a medical condition characterized by the excessive accumulation of adipose tissue, manifesting as a metabolically unhealthy state that is associated with an elevated risk of developing a spectrum of diseases[9]. Several studies have shown that individuals with overweight/obesity or increased waist circumference have a higher risk of developing BE[5,8]. In a study have found no association between BE incidence and overweight/obesity[10]. The discordant results indicate an intricate interplay between overweight/obesity and the risk of BE. The metabolically unhealthy (MU) phenotype, defined as the presence of insulin resistance, hypertension, and dyslipidemia, is commonly observed in individuals with overweight/obesity[11]. Notably, emerging evidence indicates that MU is also closely associated with chronic inflammation and increased risk of developing several diseases, including BE[12,13].

Recently, the concept of metabolically healthy overweight/obesity (MHO) has been proposed to describe those who have increased adiposity but do not have traditional cardiometabolic risk factors, such as hypertension, type 2 diabetes mellitus, and dyslipidemia, in contrast to individuals with metabolically unhealthy overweight/obesity (MUO)[11,14]. Existing evidence suggests that MHO represents a benign condition with a reduced risk of developing diseases, although conflicting findings have also been reported[15–18]. However, to date, the association between the body mass index (BMI)-metabolic status phenotype and development of BE has not been investigated. Therefore, in the present study, we evaluated the relationship of overweight/obesity and MU with the incidence of BE by using biobank data from the UK.

Methods

Study population

The UK Biobank, an ongoing national cohort study, recruited more than 500,000 individuals aged 40–70 years from 2006 to 2010 across 22 assessment centers in England, Wales, and Scotland. At baseline, the participants completed self-reported touchscreen surveys, interviews, and physical assessments, and data on demographics, lifestyle, health factors, and anthropometrics were collected. Biological samples were also collected for analysis[19]. All participants provided informed consent. The study protocol was approved by the U.K. North West Multicenter Research Ethics Committee. Data access for this study was approved by the UK Biobank Access Committee (Application 73873). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Among the 502,419 participants, those with a history of BE or esophageal cancer (n = 175), and gastric cancer (n = 177) were excluded. We further excluded 97,985 participants without metabolic indicators (n = 224,205) and missing BMI data (n = 1574). A total of 402,510 participants were included in the final analysis (Fig. 1).

Data collection and measurements

During participant recruitment, a detailed touchscreen questionnaire was used to collect information on medical history, lifestyle habits, and sociodemographic characteristics. The questionnaire included a self-reported medical history of diseases such as hypertension (I10–13 and I15), type 2 diabetes mellitus (E10–14), and

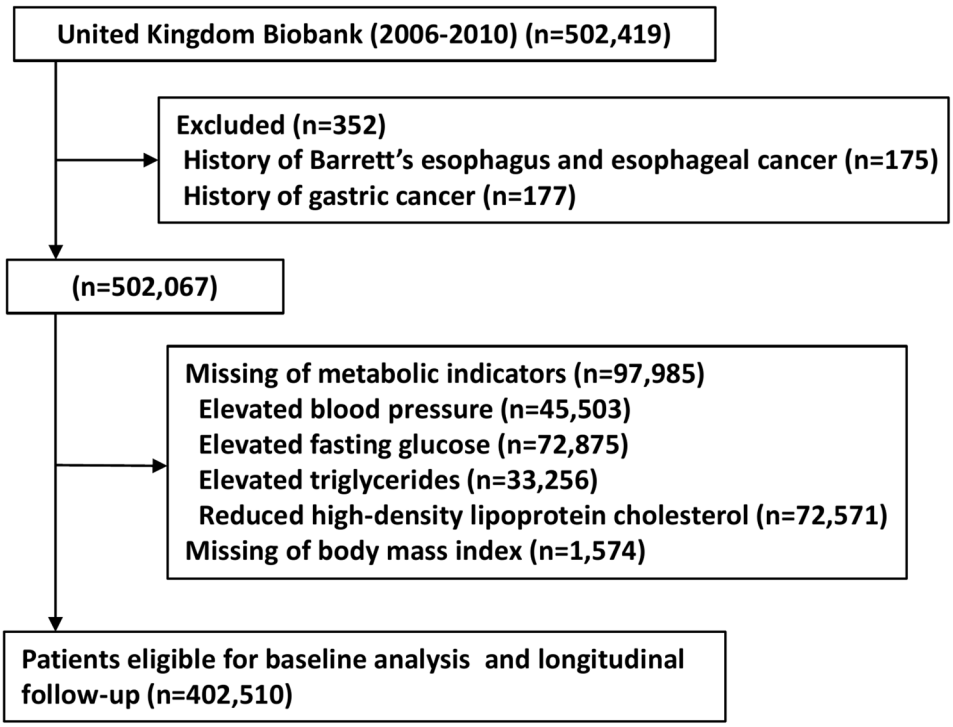


Fig. 1. Flow diagram of the study subjects.

gastroesophageal reflux disease (K21), which were assessed based on self-reported information or International Classification of Diseases-10 (ICD-10) codes. Smoking and alcohol consumption habits were categorized as 'never' or 'ever.' Annual household income was divided into four categories: (1) less than €18,000; (2) €18,000 to €30,999; (3) €31,000 to €51,999; and (4) more than €52,000. Physical activity was measured in metabolic equivalent task (MET) minutes per week and categorized into three groups (< 600, 600–3000, and > 3000 min/week) based on walking, moderate activity, and vigorous activity. Trained staff performed physical measurements of the participants. Height and weight were measured using a Seca 202 height meter while the participants were barefoot. BMI was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured using an Omron 705 IT electronic sphygmomanometer.

After overnight fasting, venous blood samples were collected to measure hemoglobin, creatinine, total protein, albumin, glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hs-CRP) levels. Laboratory parameters were measured using established protocols and standardized equipment from Beckman Coulter (UK). Further details on the methodology and specific protocols can be obtained from the UK Biobank website (https://biobank.ctsu.ox.ac.uk/showcase).

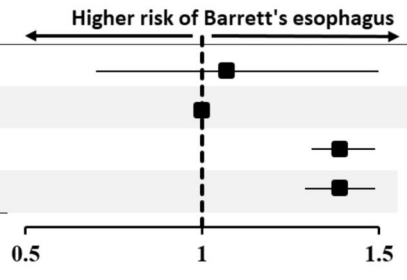
Assessment of metabolically unhealthy and overweight/obesity

In this study, "metabolically healthy (MH)" was defined as the absence of all of the following metabolic indicators[20]: (1) High blood pressure (≥ 130/85 mmHg), diagnosis of hypertension, or use of anti-hypertensive medications; (2) Elevated fasting blood sugar (≥ 125 mg/dL), diagnosis of type 2 diabetes, or use of anti-diabetes medications; (3) High triglycerides (≥ 150 mg/dL) or use of fibrate medications; (4) HDL-C levels ≤ 40 mg/dL for men and ≤ 50 mg/dL for women, or use of lipid-lowering medications. Conversely, "metabolically unhealthy (MU)" status was defined as having at least one of the above risk factors. Overweight/obesity was defined based on the World Health Organization's BMI cut-off of ≥ 25.0 kg/m^2. The validity of these definitions was further supported by the study results. As shown in Fig. 2, the risk of incident BE increased significantly in participants with one or more metabolic indicators and BMI ≥ 25.0 kg/m^2. Consequently, the participants were categorized into four different groups: (1) metabolically healthy non-overweight/obesity (MHNO, BMI < 25.0 kg/m^2 without MU), (2) metabolically unhealthy non-overweight/obesity (MUNO, BMI < 25.0 kg/m^2 with MU), (3) metabolically healthy overweight/obesity (MHO, BMI ≥ 25.0 kg/m^2 without MU), and (4) metabolically unhealthy overweight/obesity (MUO, BMI ≥ 25.0 kg/m^2 with MU).

Outcome assessment

The primary outcome of interest was BE occurrence as defined by the 10th revision of the International Classification of Diseases (ICD-10) code (K22.7). Outcome assessments were performed from enrollment to final follow-up. The follow-up period was determined based on data availability in the UK Biobank and defined as the period from the date of study enrollment to the date of the last available data for each participant, which was February 28, 2021, for participants from England and Scotland and February 28, 2018, for participants from Wales.

Body mass index	No. of Events	No. of Patients	Hazard Ratio (95% CI)	P-value
<18.5 kg/m²	21	2,049	1.07 (0.70–1.65)	0.750
18.5–24.9 kg/m²	1,369	129,319	Reference	-
25.0–29.9 kg/m²	3,018	171,408	1.39 (1.31–1.49)	<0.001
≥30 kg/m²	1,787	99,734	1.39 (1.29–1.49)	<0.001



No. of Metabolic factors	No. of Events	No. of Patients	Hazard Ratio (95% CI)	P-value
0	593	64,718	Reference	-
1	2,110	147,596	1.34 (1.22–1.46)	<0.001
2	2,114	118,168	1.49 (1.36–1.63)	<0.001
3	1,085	58,174	1.48 (1.34–1.64)	<0.001
4	316	15,389	1.56 (1.36–1.80)	<0.001

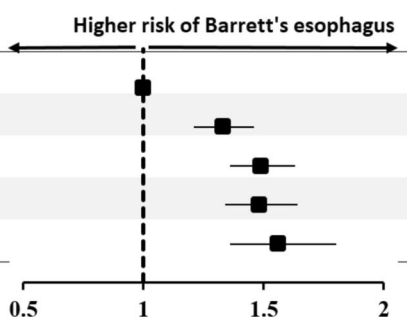


Fig. 2. Hazard ratios for the occurrence of Barrett's esophagus according to according to body mass index and number of metabolic factors. In adjusted model, covariates including age, sex, race, smoking, alcohol habits, and history of gastroesphageal reflux disease. No, number; CI, confidence interval.

Statistical analysis

The baseline characteristics were summarized using descriptive statistics (mean, standard deviation [SD], count, percentage, median, and inter-quartile range [IQR]). Differences between continuous and categorical covariates according to the BMI (≥ 25 vs. < 25 kg/m^2) and metabolic status were compared using ANOVA, chi-square test, or Kruskal–Wallis test. The cumulative incidence of BE according to the BMI and metabolic status was estimated using the Kaplan–Meier method and compared using the log-rank test. Survival time was defined as the time from enrollment to the onset of BE. The scaled Schoenfeld residual method was used to verify the proportional hazards assumption[21].

The risk of BE development was assessed using multivariate Cox proportional hazard regression models: Model 1 (crude risk) without adjustment; Model 2 was adjusted for age, sex, race, smoking, and alcohol consumption; and Model 3 was further adjusted for history of GERD in addition to the Model 2 covariates. We evaluated the proportional hazards assumption by examining log (–log [survival]) plots of the survival function. In Model 4, we performed a separate analysis using a logistic regression model with inverse probability of treatment weighting (IPTW) derived from the baseline covariates included in Model 3 to address potential selection bias and confounding[22]. After IPTW adjustment, the maximum pairwise standardized difference for any variable was < 0.1, indicating good covariate balance (Table S1). The results of multivariate Cox proportional hazards regression and IPTW models are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Differences in the risk of BE among the four groups were further assessed using the Bonferroni method[23]. We also performed a sensitivity analysis using a BMI cutoff value of 30.0 kg/m^2 to test the robustness of the primary results. All the statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

Results

Demographic and clinical characteristics

Baseline characteristics according to the BMI and/or metabolic status are shown in Table 1. Of the 402,510 participants, 39,281 (9.7%), 92,000 (22.9%), 25,297 (6.3%), and 245,932 (61.1%) were classified as MHNO, MUNO, MHO, and MUO, respectively. The mean age of the participants was 56.6 years and 53.6% were men. The prevalence of hypertension, type 2 diabetes, and GERD was 33.5%, 5.6%, and 7.3%, respectively. Regardless of the BMI, individuals with MU were older and had significantly higher blood pressure, unfavorable lipid profiles, and higher levels of inflammatory markers than those with MH. These differences were more pronounced in the MUO group compared to the other group. However, the differences in the baseline characteristics between the MUNO and MHO groups were not significant.

Body mass index, metabolically unhealthy, and risk of Barrett's esophagus

First, we assessed the independent association of BMI and metabolic status with the risk of BE development. During 5,374,032.7 person-years of follow up, BE occurred in 6,195 (1.5%) individuals. The overall incidence rate was 1.2 per 1000 person-years (Table 2). As expected, the incidence of BE was significantly higher in individuals with a BMI ≥ 25 kg/m^2 and those with MU. Multivariable Cox proportional analyses revealed a 1.35-fold increased risk (HR 1.35; 95% CI 1.31–1.48) for individuals with BMI ≥ 25 kg/m^2 and 1.43-fold increased risk (HR 1.43; 95% CI 1.31–1.56) for those with MU (Model 3). These associations remained consistent even after adjusting for potential confounding factors using IPTW (Model 4).

Risk of Barrett's esophagus according to the presence of the four metabolic phenotypes

We further analyzed the risk of incident BE according to a BMI cutoff value of 25.0 kg/m^2 and/or metabolically unhealthy. The incidence rates of BE in the MHNO, MUNO, MHO, and MUO groups were 0.5, 0.9, 0.9, and 1.4 per 1000 person-years, respectively (Table 3). The MUO group had a significantly higher incidence rate than the other groups (all p-values < 0.001). Interestingly, the incidence rates of BE in the MUNO and MHO groups were similar (p-value = 0.91). Similarly, the cumulative incidence rate of BE was significantly higher in the MUO group than in the other groups (all $p < 0.001$) (Fig. 3). However, the incidence rates of BE in the MUNO and MHO groups were not significantly different (p-value = 0.88). In multivariate Cox regression analysis, the MUO group had a 2.62–fold (95% CI 2.32–2.96) increased risk of BE development compared to the MHNO group (Model 1). This risk remained significantly elevated at 1.88-fold (95% CI 1.67–2.13) even after adjusting for confounding factors (Model 3). Both the MUNO and MHO groups exhibited similar risks of BE development compared to the MHNO group, with HRs of 1.73 (95% CI 1.51–1.97) and 1.78 (95% CI 1.51–2.09), respectively (Model 1). After adjustment for confounding factors, the risk of incident BE was 1.45-fold (95% CI 1.27–1.66) and 1.57-fold (95% CI 1.33–1.84) higher in the MUNO and MHO groups, respectively (Model 3). These findings were consistent with the analysis using IPTW to minimize the influence of confounding factors (Model 4). Intergroup comparison with multiple Bonferroni corrections also revealed that the risk of BE development was consistently higher in individuals with MUO than in the other groups (all $p < 0.001$) (Table 4). Importantly, the risk of BE development did not differ significantly between the MHO and MUNO groups: (HR, 1.08; 95% CI 0.95–1.22; corrected p = 1.000). These results indicate that a higher BMI and metabolic unhealthy status independently increase the risk of BE, and their combined effect is synergistic.

Sensitivity analysis

To assess the robustness of our primary findings, we conducted several sensitivity analyses. First, we used a different BMI cutoff value (≥ 30.0 kg/m^2), finding that individuals with BMI ≥ 30.0 kg/m^2 exhibited a 1.11-fold increased risk of BE development (HR 1.11; 95% CI 1.05–1.18) (Table S2). The risk of BE was significantly higher in the MUNO, MHO, and MUO groups than in the MHNO group (Table S3). Furthermore, after statistical

		BMI < 25.0 kg/m²		BMI ≥ 25.0 kg/m²		
	Overall	MHNO	MUNO	MHO	MUO	*p*-value
Number of participants	402,510	39,281	92,000	25,297	245,932	
Age, mean (SD)	56.6 (8.0)	52.3 (7.8)	57.3 (7.9)	52.7 (7.8)	57.5 (7.9)	< 0.001
Sex, n (%)						< 0.001
Male	215,785 (53.6)	29,652 (75.5)	55,343 (60.2)	16,875 (66.7)	113,915 (46.3)	
Female	186,725 (46.4)	9629 (24.5)	36,657 (39.8)	8422 (33.3)	132,017 (53.7)	
Race, n (%)						< 0.001
White	378,950 (94.2)	37,227 (94.9)	86,943 (94.6)	23,574 (93.3)	231,206 (94.1)	
Non-white	23,154 (5.7)	2020 (5.2)	4985 (5.4)	1700 (6.8)	14,449 (5.9)	
Hypertension, n (%)	134,781 (33.5)	0 (0.0)	26,291 (28.6)	0 (0.0)	108,490 (44.1)	< 0.001
Type 2 diabetes, n (%)	22,549 (5.6)	0 (0.0)	2561 (2.8)	0 (0.0)	19,988 (8.1)	< 0.001
GERD, n (%)	29,534 (7.3)	1303 (3.3)	5064 (5.5)	1394 (5.5)	21,773 (8.9)	< 0.001
Smoking, n (%)						< 0.001
Never	218,399 (54.5)	24,316 (62.1)	52,753 (57.6)	14,561 (57.8)	126,769 (51.8)	
Ever	182,096 (45.5)	14,839 (37.9)	38,855 (42.4)	10,636 (42.2)	117,766 (48.2)	
Alcohol, n (%)						< 0.001
Never	17,756 (4.4)	1357 (3.5)	4001 (4.4)	923 (3.7)	11,475 (4.7)	
Ever	383,771 (95.6)	37,854 (96.5)	87,783 (95.6)	24,325 (96.3)	233,809 (95.3)	
Income, n (%)						< 0.001
< 18,000 €	78,630 (22.9)	4911 (14.2)	17,456 (22.4)	3502 (15.7)	52,761 (25.3)	
18,00,030,999 €	87,502 (25.5)	7116 (20.6)	20,529 (26.3)	4817 (21.6)	55,040 (26.4)	
31,000–51,999 €	89,335 (26.0)	9629 (27.9)	20,132 (25.8)	6414 (28.8)	53,160 (25.5)	
> 52,000 €	88,202 (25.7)	12,912 (37.4)	19,838 (25.4)	7548 (33.9)	47,904 (22.9)	
Metabolic equivalent task, n (%)						< 0.001
< 600 min/week	61,124 (18.8)	4678 (14.1)	11,125 (14.9)	3741 (17.8)	41,580 (21.1)	
600–3000 min/week	163,897 (50.4)	17,615 (53.2)	38,132 (54.1)	10,900 (51.8)	97,250 (49.6)	
> 3000 min/week	100,036 (30.8)	10,833 (32.7)	25,569 (34.2)	6397 (30.4)	57,237 (29.2)	
Body mass index (kg/m², SD)	27.5 (4.9)	22.4 (1.7)	22.9 (1.6)	27.9 (2.8)	29.9 (4.2)	< 0.001
Systolic BP (mmHg, SD)	137.8 (18.5)	117.2 (8.4)	139.8 (17.9)	119.7 (7.3)	142.4 (17.4)	< 0.001
Diastolic BP (mmHg, SD)	82.2 (10.1)	72.3 (6.3)	81.5 (9.6)	74.9 (5.8)	85.0 (9.7)	< 0.001
Hemoglobin (g/dL, SD)	14.2 (1.2)	13.6 (1.1)	14.0 (1.2)	13.8 (1.2)	14.4 (1.2)	< 0.001
eGFR (mL/min per 1.73 m², SD)	94.5 (13.2)	98.9 (11.4)	95.7 (12.5)	96.5 (12.1)	93.2 (13.6)	< 0.001
Total protein (mmol/L, SD)	72.5 (4.1)	71.9 (4.0)	72.6 (4.3)	71.9 (4.0)	72.7 (4.1)	< 0.001
Albumin (mmol/L, SD)	38.9 (3.3)	39.5 (3.3)	39.3 (3.3)	38.8 (3.2)	38.7 (3.3)	< 0.001
Glucose (mg/dL, SD)	92.4 (22.5)	84.3 (8.3)	91.3 (18.9)	85.6 (7.7)	94.9 (25.6)	< 0.001
Lipid profiles						
Total cholesterol (mg/dL, SD)	219.8 (44.3)	214.8 (36.7)	222.6 (43.5)	219.2 (36.8)	219.6 (46.3)	< 0.001
Triglyceride (mg/dL, SD)	155.2 (91.1)	87.9 (26.9)	133.3 (71.7)	98.3 (27.4)	179.9 (98.1)	< 0.001
HDL-C (mg/dL, SD)	55.9 (14.8)	66.7 (13.3)	61.1 (15.9)	61.4 (11.9)	51.7 (13.1)	< 0.001
LDL-C (mg/dL, SD)	137.4 (33.7)	128.9 (28.3)	137.1 (32.9)	136.2(29.0)	138.9 (34.9)	< 0.001
hs-CRP (mg/L, interquartile ranges)[a]	1.34 (0.66–2.79)	0.61 (0.34–1.19)	1.18 (0.63–2.30)	0.86 (0.45–1.73)	1.79 (0.93–3.48)	< 0.001

Table 1. Baseline characteristics of study patients in four phenotypes classified by BMI and/or metabolic status. Values for categorical variables are provided as numbers (percentages); values for continuous variables are provided as means (standard deviations) or medians (interquartile ranges). eGFR was calculated using the CKD-EPI equation. Conversion factors for units: cholesterol in mg/dL to mmol/L × 0.02586. Smoking was defined as never, former, or current. MHNO, metabolically healthy non-overweight/obesity; MUNO, metabolically unhealthy non-overweight/obesity; MHO, metabolically healthy overweight/obesity; MUO, metabolically unhealthy overweight/obesity; GERD, gastroesophageal reflux disease; €, euro; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation. [a]Variables were compared using the Kruskal–Wallis test.

adjustment using Bonferroni method, MUNO and MHO demonstrated a similar risk of BE development (HR 1.12; 95% CI 0.88–1.43; corrected $p = 1.000$) (Table S4). We also defined obesity using the waist-to-hip ratio (WHR) and found consistent results (Tables S5, S6). Additionally, we examined differences according to sex and BMI-metabolic status phenotype (Table S7). The results of these sensitivity analyses consistently supported

		BMI category		Metabolic status	
		BMI < 25.0 kg/m^2	BMI ≥ 25.0 kg/m^2	Healthy	Unhealthy
Patient-years		1,758,775.8	3,615,256.9	866,673.2	4,507,359.5
Incidence of outcome, n/n		1388/131,281	4807/271,229	591/64,578	5604/337,932
Incidence rate per 1000 patients-years		0.7	1.3	0.7	1.2
Model 1	HRs (95% CI)	1.00 (Reference)	1.68 (1.59–1.79)	1.00 (Reference)	1.82 (1.68–1.98)
	P-value	–	< 0.001	–	< 0.001
Model 2	HRs (95% CI)	1.00 (Reference)	1.51 (1.42–1.60)	1.00 (Reference)	1.55 (1.43–1.69)
	P-value	–	< 0.001	–	< 0.001
Model 3	HRs (95% CI)	1.00 (Reference)	1.39 (1.31–1.48)	1.00 (Reference)	1.43 (1.31–1.56)
	P-value	–	< 0.001	–	< 0.001
Model 4	HRs (95% CI)	1.00 (Reference)	1.35 (1.27–1.43)	1.00 (Reference)	1.18 (1.07–1.30)
	P-value	–	< 0.001	–	< 0.001

Table 2. Hazard ratios for the incidence of Barrett's esophagus according to the body mass index category and metabolic status. Model 1: a crude analysis without adjustment. Model 2: adjusted by age, sex, race, smoking, and alcohol habits. Model 3: adjusted model 2 plus history of gastroesophageal reflux disease. Model 4: weighted hazard ratio after inverse probability of treatment weighting for confounding factor in model 3. BMI, body mass index; HRs, hazard ratios; CI, confidence interval.

	Overall	MHNO	MUNO	MHO	MUO
Patient-years	5,374,032.7	527,751.6	1,231,024.2	338,921.6	3,276,335.2
Incidence of outcome, n/n	6195/402,510	276/39,281	1112/92,000	315/25,297	4492/245,932
Incidence rate per 1000 person-years	1.2	0.5	0.9	0.9	1.4
Model 1	HRs (95% CI)	1.00 (Reference)	1.73 (1.51–1.97)	1.78 (1.51–2.09)	2.62 (2.32–2.96)
	P-value	–	< 0.001	< 0.001	< 0.001
Model 2	HRs (95% CI)	1.00 (Reference)	1.53 (1.34–1.75)	1.66 (1.41–1.95)	2.14 (1.89–2.42)
	P-value	–	< 0.001	< 0.001	< 0.001
Model 3	HRs (95% CI)	1.00 (Reference)	1.45 (1.27–1.66)	1.57 (1.33–1.84)	1.88 (1.67–2.13)
	P-value	–	< 0.001	< 0.001	< 0.001
Model 4	HRs (95% CI)	1.00 (Reference)	1.38 (1.19–1.57)	1.52 (1.27–1.77)	1.66 (1.40–1.91)
	P-value	–	< 0.001	< 0.001	< 0.001

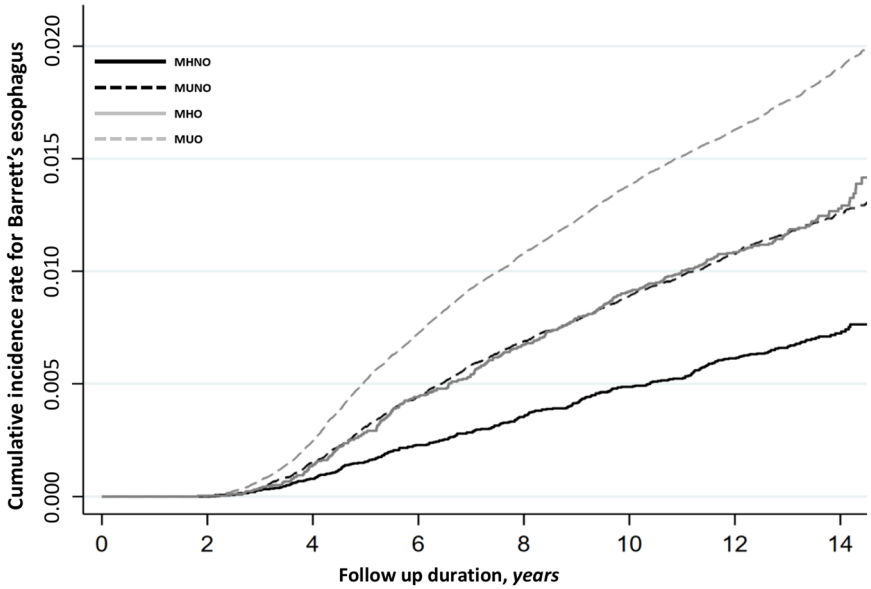
Table 3. Hazard ratios for the incidence of Barrett's esophagus among 4 metabolic subtypes classified by the BMI cut off 25.0 kg/m^2 and/or metabolically unhealthy. Model 1: a crude analysis without adjustment. Model 2: adjusted by age, sex, race, smoking, and alcohol habits. Model 3: adjusted model 2 plus history of gastroesophageal reflux disease. Model 4: weighted hazard ratio after the inverse probability of treatment weighting to confounders in model 3. BMI, body mass index; MHNO, metabolically healthy non-overweight/obesity; MUNO, metabolically unhealthy non-overweight/obesity; MHO, metabolically healthy overweight/obesity; MUO, metabolically unhealthy overweight/obesity; HRs, hazard ratios; CI, confidence interval.

our primary findings, emphasizing the synergistic effect of higher BMI and metabolic unhealthy status on the risk of incident BE.

Discussion

The present study investigated the association among overweight/obesity, MU status, and incidence of BE using data from the UK Biobank database. The major findings were as follows: (1) Study participants were categorized into four BMI-metabolic status phenotypes, including the MHNO (9.8%), MUNO (22.9%), MHO (6.3%), and MUO (61.1%), which were compared for the risk of developing BE during follow-up. (2) Individuals who were overweight/obese had a significantly greater risk of developing BE in both the MHO and MUO groups than in the MHNO group. (3) Interestingly, individuals in the MUNO group were also at an increased risk of BE compared with those in the MHNO group, and those in the MUO group had the highest risk of developing BE, indicating that overweight/obesity and MU both synergistically contribute to the occurrence of BE.

According to the 2016 World Health Organization statistics, being overweight affects up to 1.9 billion adults aged 18 years and older, with over 650 million individuals classified as obese[24]. This surge in the global prevalence of obesity is closely associated with MU and has emerged as a pressing public health issue. Overweight/obesity, especially central obesity, has been reported to be a risk factor for the development of BE[5,8,25]. The association between overweight/obesity and BE is multifaceted, involving mechanisms related to GERD, hormonal signaling, chronic inflammation, microbial dysbiosis, and inadequate immune response[5,26–29]. Central obesity amplifies



Number at risk								
MHNO	39,281	39,282	39,250	39,191	39,138	38,772	37,536	12,222
MUNO	92,000	92,000	91,861	91,590	91,360	90,014	86,529	27,980
MHO	25,297	25,296	25,262	25,185	25,126	24,876	24,106	7,752
MUO	245,932	245,926	245,326	244,151	243,266	238,535	228,275	75,527

Fig. 3. Cumulative incidence rate for Barrett's esophagus according to metabolic phenotypes. MHNO, metabolically healthy non-overweight/obesity; MUNO, metabolically unhealthy non-overweight/obesity; MHO, metabolically healthy overweight/obesity; MUO, metabolically unhealthy overweight/obesity.

	MHNO	*P*-value	MUNO	*P*-value	MHO	*P*-value	MUO	*P*-value
MHNO	–	–	1.42 (1.24–1.63)	< 0.001	1.54 (1.31–1.81)	< 0.001	1.90 (1.68–2.15)	< 0.001
MUNO	0.70 (0.61–0.80)	< 0.001	–	–	1.08 (0.95–1.22)	1.00	1.30 (1.22–1.39)	< 0.001
MHO	0.65 (0.55–0.77)	< 0.001	0.93 (0.82–1.05)	1.00	–	–	1.21 (1.08–1.36)	0.01
MUO	0.53 (0.47–0.60)	< 0.001	0.77 (0.72–0.82)	< 0.001	0.83 (0.74–0.93)	0.01	–	–

Table 4. Statistical adjustments with multiple comparisons for risk of Barrett's esophagus according to the body mass index category and metabolic status. Multiple comparisons between the groups were performed using the Bonferroni's correction method. The MUO group exhibits a statistically significant higher risk of BE occurrence compared to the MHNO, MUNO, and MHO groups. Additionally, there is no significant difference in BE occurrence between the MUNO and MHO groups. This indicates that a metabolic unhealthy status combined with overweight/obesity synergistically increases the risk of BE occurrence. MHNO, metabolically healthy non-overweight/obesity; MUNO, metabolically unhealthy non-overweight/obesity; MHO, metabolically healthy overweight/obesity; MUO, metabolically unhealthy overweight/obesity.

intragastric pressure, disturbs normal sphincter function, and delays gastric emptying, culminating in a higher propensity for GERD and increased risk of BE[5,26,28]. Moreover, adipose tissue, particularly visceral fat located in the abdomen, secretes various hormones and inflammatory substances. These hormones, including leptin and adiponectin, can affect the function of the lower esophageal sphincter and contribute to the development of GERD or BE[27,30,31]. These findings suggest a potential indirect pathway connecting increasing adiposity to the development of BE[29]. In contrast, some studies have shown that overweight/obesity has an unclear role in BE development in patients with GERD[10]. Although various theories have suggested that overweight/obesity may increase the risk of BE, it is still difficult to draw reliable conclusions. In particular, the relationship between BMI, but not central obesity, and the risk of BE remains controversial. In this study using data from the UK Biobank database, individuals with overweight/obesity (both BMI ≥ 25 kg/m^2 and ≥ 30 kg/m^2) exhibited a higher risk of developing BE than those with normal weight.

The components required for identifying MU are not clearly defined yet, and vary among studies. Regarding the contribution of metabolic status in determining the risk of BE, this study found that the presence of even a single metabolic risk factor was associated with an increased incidence of BE. Metabolic syndrome is a cluster of common pathologies, and we defined MU status as the presence of one or more metabolic risk factors.

Interestingly, the risk of BE was significantly higher in individuals with MUNO than in those with MHNO. Moreover, the highest risk of developing BE was observed in the MUO group, further emphasizing that MU has a substantial impact on BE and should not be overlooked.

In general, overweight/obesity and impaired metabolism are tightly linked phenotypical traits, and MU is highly prevalent in obese individuals[32]. Although previous studies have shown that central obesity is related to the occurrence of BE, the role of MU, independent of overweight/obesity, in the development of BE remains unclear. A notable finding of our study was that MU was significantly associated with an increased risk of developing BE, independent of being overweight/obese. Inflammation emerges as a plausible reason for this finding, with its potential involvement in both the initiation and advancement of BE, by contributing to its pathogenesis and progression[13,33,34]. Given the detrimental effects of inflammation on cholesterol metabolism, insulin resistance, and vascular remodeling, MU may reflect a preclinical hyper-inflammatory state that predisposes individuals to BE[35,36]. This notion is supported by our observation that the presence of MU was associated with a higher hs-CRP level, a marker of systemic inflammation, in both individuals with BMI < 25.0 kg/m^2 and those with BMI ≥ 25 kg/m^2. However, the precise nature of this association has not been explored, necessitating further research to elucidate the underlying mechanisms.

While overweight/obesity and metabolic risk factors commonly exhibit interconnectedness, they may also coexist independently in certain individuals, and their clinical implications can differ based on the BMI-metabolic status phenotypes. Notably, a distinct subtype of overweight/obesity known as MHO has received significant attention due to its relatively favorable clinical outcomes regarding obesity-related diseases, such as cardiovascular disease[37]. Furthermore, not all individuals with a lean physique exhibit a healthy metabolic profile, and the concept of MUNO has been proposed to explain the heterogeneous nature of overweight/obesity[37]. Individuals with MHO and MUNO exhibit insulin sensitivity, lipid pathways, and inflammatory profiles that are opposite to those predicted for the overweight/obesity status. Although there is sufficient evidence that MHO represents a relatively benign state with an attenuated risk of developing various illnesses, discordant research outcomes have been reported[15–17]. This suggests the need for a more comprehensive investigation into how MU and overweight/obesity distinctly impact various diseases. However, little is known about the BMI-metabolic status phenotypes in populations with BE. Intriguingly, the present study demonstrated that the risk of BE was significantly greater in individuals with MUNO and MHO than in those with MHNO, suggesting that in the presence of overweight/obesity, metabolic health may not be a benign phenotype with respect to the development of BE.

The results of our study underscore the importance of metabolic health and maintaining an optimal body weight to mitigate the risk of developing BE. Both metabolic disorders and obesity can increase the risk of developing BE. Hence, proactive initiatives targeting weight reduction, consistent physical activity, and adherence to a nutritious diet are advisable as preventive measures against the onset of BE. Given that body weight, exercise, and diet modification can positively influence metabolic health[38], the beneficial effect may also extend to individuals who are not overweight or obese. We further evaluated the independent association of BMI and metabolic status with the risk of BE, adjusting for confounding factors including Total metabolic equivalent task (MET) in addition to model 3 (data not shown). The results remained consistent with our initial finding, therefore, maintaining physical activity is highly beneficial to prevent BE.

Our study has some limitations. First, we could not confirm a causal relationship between MU and BE because of the observational nature of the study. Second, the primary outcome of our study was based on ICD codes. Thus, issues regarding diagnostic accuracy and overestimation or underestimation of BE incidence can occur in such a large-scale population-based study. However, the incidence rate of BE reported in this study (6,195/402,510, 1.5%) does not contradict prior estimates of BE incidence (average estimate of 0.5–2% in the general population)[4,39,40]. Third, BMI and metabolic conditions can change overtime, potentially influencing the risk of developing BE in different directions. The present study did not analyze possible changes in the BMI-metabolic status phenotypes during the follow-up period owing to the unavailability of relevant data. It is challenging to clearly distinguish whether the MHO group has independent characteristics or if they are a group at high risk of progressing to MUO. However, this is a cross-sectional study, we can observe the participants' status at the time of study enrollment. Fourth, MU is a complex condition comprising diverse clinical manifestations such as increased blood pressure, insulin resistance, dyslipidemia, diet and systemic inflammatory conditions. However, we could not independently assess the specific contributions of these components to BE development. These components may act together to promote an inflammatory environment that predisposes individuals to BE. Fifth, additional analyses based on certain epidemiologic factors may be required. The UK Biobank includes individuals from diverse ethnic backgrounds, and BMI classifications for Asians differ from those of other populations. Although we conducted a subgroup analysis according to ethnicity, the results were inconclusive (data not shown). This may be due to the challenge of obtaining detailed ethnic information within groups that include Asians and other ethnicities, as well as the low incidence of BE within these groups. Additionally, while the overall trend shows similar risk increases in both sexes (Table S7), the significant interaction suggests that the magnitude of these effects differs by sex (data not shown). This indicates that although both males and females experience an increased risk of BE with weight and metabolic abnormalities, the extent of this increase is influenced by the interaction between sex and phenotypes. These findings highlight the importance of considering sex-specific factors in the analysis and interpretation of BE risk factors. Further research is needed to confirm these findings and to explore the biological or behavioral reasons behind these sex and ethnic differences. Finally, the study population was limited to individuals in the UK, and the UK Biobank study has been criticized for "healthy volunteer" selection bias[41]. Therefore, our findings may not be generalizable to other populations.

In conclusion, our results showed that both overweight/obesity and MU are independently associated with an increased risk of BE. Furthermore, the risk of BE was significantly higher in individuals with both overweight/obesity and MU than in those with either overweight/obesity or MU alone. Our findings provide valuable insight

into the complex relationship between overweight/obesity and MU, leading to the development of BE, and may help to guide future efforts to prevent and manage BE.

Data availability

Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information (contact to HY).

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Author contributions

HY, and CWH contributed to study conception and design; DHJ, YJK, HBK, NS, JTP, SHH, TY, SK, HY, and CWH contributed to the study design, direction, and guidance; DHJ, HBK, NS, HY, and CWH contributed to analysis of clinical data and manuscript writing; DHJ, YJK, HBK, NS, JTP, SHH, TY, SK, HY, and CWH provided statistical input and analysis; DHJ, YJK, HBK, NS, JTP, SHH, TY, SK, HY, and CWH approved final of the article.

Competing interests

The authors declare no competing interests.

Additional information

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