Published in final edited form as:

Cancer Epidemiol. 2016 June ; 42: 9–14. doi:10.1016/j.canep.2016.02.008.

Metabolic syndrome in relation to Barrett's esophagus and esophageal adenocarcinoma: results from a large population-based case-control study in the Clinical Practice Research Datalink

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Abstract

Gastroesophageal reflux disease (GERD) causes local chronic inflammation that increases risks of Barrett's esophagus (BE) and esophageal adenocarcinoma (EA), yet symptomatic GERD is absent in approximately half of all such patients. Obesity exacerbates GERD and is also a component of metabolic syndrome (MetS). We evaluated the hypothesis that MetS is a GERD-independent mechanism by which obesity is associated with increased risks of BE and EA using data from the UK Clinical Practice Research Datalink. BE cases (n=10,215) and EA cases (n=592) were each individually matched to five population controls based on age, sex, and general practice. MetS was defined as occurrence of at least three of the following: obesity, type 2 diabetes, hypertension, and high cholesterol. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. MetS was marginally associated with BE (OR=1.12, 95%CI 1.00–1.25). Similar effects were found for the individual component factors of obesity, hypertension, and high cholesterol. History of GERD modified the association (p-effect modification < 1E 5), with the MetS-BE association confined to patients without a history of GERD (OR=1.33, 95%CI 1.12–1.58). No association between MetS and risk of EA was detected in the main or stratified analyses. In this large population-based case-control study, individuals with MetS had a marginally increased risk of BE in the absence of GERD. The systemic inflammatory state (MetS) may represent a reflux-independent inflammatory pathway that increases the risk of BE. MetS did not increase risk of EA in this study population.

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²Manuscript submitted for publication

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institutes of Health.

There are no financial disclosures from any of the authors.

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Keywords

Barrett Esophagus; Esophageal Cancer; Metabolic Syndrome X; Obesity; Gastroesophageal Reflux

INTRODUCTION

Chronic inflammation has a central role in the etiology of esophageal adenocarcinoma (EA) and the precursor lesion Barrett's esophagus (BE). Evidence suggests that chronic inflammation triggered by gastroesophageal reflux disease (GERD) not only predisposes to developing BE, but that the ensuing proinflammatory state¹ and oxidative stress² have roles in malignant transformation³.

Although GERD is a key risk factor of EA⁴⁻⁶, symptomatic GERD is infrequent or absent in 40–48% of people who develop EA^{6,7}. Likewise, although GERD is a known risk factor of BE⁸⁻¹⁰, more than half of patients diagnosed with BE have an indication for endoscopy other than GERD¹¹. These data suggest that other inflammatory mechanisms may exist in the pathogenesis of BE and EA.

Another significant risk factor of BE and EA is abdominal obesity, which causes a state of systemic inflammation, characterized by increased circulating proinflammatory cytokines including C-reactive protein, leptin, interleukin-6, and tumor necrosis factor- α . The proinflammatory effects of excess adipose tissue are a hallmark of MetS¹², which itself is a cluster of metabolic disorders that includes abdominal obesity, hypertension, lowered high density lipoprotein (HDL) cholesterol, elevated triglycerides, and elevated fasting glucose¹³. MetS is a better predictor of total mortality than its individual components¹⁴, and may increase the risk of BE¹⁵⁻¹⁸ and EA¹⁹.

We recently demonstrated that MetS increased risks of BE¹⁸ and EA¹ in an older-aged US population (SEER-Medicare), associations driven by and confined to those without a history of GERD. We proposed that in those without symptomatic GERD, systemic inflammation—represented by MetS—increases the risk for normal esophageal tissues to develop metaplasia and eventually cancer.

The few studies that have evaluated the association of MetS in relation to BE or EA have either not been population-based¹⁵⁻¹⁷, did not include the full age-range of patients¹⁸ or did not investigate potential effect-modification by GERD¹⁹⁻²¹. Therefore, using data collected prospectively in the Clinical Practice Research Datalink (CPRD), which contains longitudinal medical records of virtually all UK primary care events of >8 million subjects of all ages, we investigated MetS in relation to risks of BE and EA separately and evaluated whether GERD was an effect-modifier of these relationships.

¹Manuscript submitted for publication

METHODS

Data Source

The CPRD, formerly known as the General Practice Research Database (GPRD), is one of the world's largest primary care electronic medical record databases. The CPRD contains longitudinal medical records of health care events including diagnoses, referrals, prescriptions, diagnostic testing, and lifestyle information for participating primary care practices and linkage to cancer registries in the UK since 1989. In addition, as part of the UK healthcare system, medical diagnoses and treatments at locations other than the General Practice are reported back to such and electronically-recorded in the CPRD. Diagnoses in the CPRD are identified by READ codes and generally have high validity, especially for chronic diseases including cancer²²⁻²⁴. The database has been described in extensive detail elsewhere²⁵.

Study Population

Our study included all people without type 1 diabetes in the CPRD from 01/01/1992 through 05/30/2012. All subjects were required to have a minimum of three years of up-to-standard medical history in the CPRD prior to diagnosis of BE, esophageal cancer, or match date for controls. Two case groups were defined: BE and EA cases. Five population controls were incidence density matched to each BE case and, separately, to each EA case based on date of diagnosis (exact), birth year, sex, year of entry in CPRD (same as case or earlier), and general practice, with replacement between risk-sets. For cases, the date of diagnosis was deemed the "index" date. Controls were assigned the index date of their matched case.

Case Definitions

BE was defined as one or more instances of the Read Code J101611. BE cases were excluded if they had one or more instances of the non-specific "Barrett's ulcer" (J102500) prior to BE or if BE was reported by the patient at an initial GP visit (i.e. history of BE prior to start of patient record) in order to reduce the possibility of contamination of the incident BE case group with prevalent cases. Those with a history of cancer (except non-melanoma skin cancer) prior to BE were excluded. Those diagnosed with esophageal cancer within six months after their initial BE diagnosis were also excluded because this short time interval infers concurrent diagnoses, and incident esophageal cancer is a distinct case group in this study design. We also conducted a sensitivity analysis in which the BE case definition required two or more BE diagnosis codes for inclusion.

Individuals with an esophageal cancer READ code were identified as potential EA cases. Since there are two major histologies of esophageal cancer, squamous cell and adenocarcinoma, each with distinct localization and etiologies, we required either a prior diagnosis of BE or a READ histology code (BB5..00; BB5..11; BB52.00) for "adenocarcinoma" $\pm$ one month from the esophageal cancer diagnosis date. EA cases were excluded if a READ histology code for "squamous cell" was recorded within one month of the esophageal cancer diagnosis date.

Control Definition

Potential population control subjects for the BE and EA case groups were excluded if they had any instance of BE (J101611) or “Barrett’s ulcer” of the esophagus (J102500) prior to their index date or if BE was reported by the patient and documented at an initial GP visit (i.e. history of BE).

All potential controls were required to be cancer-free (excluding non-melanoma skin cancer) up to their index date and not diagnosed with esophageal cancer during the six months following their index date (as a balance to the BE case group selection criterion).

Definition of Metabolic Syndrome

MetS was defined using the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)²⁶ which is the presence of at least three of the following conditions: abdominal obesity, hypertension, lowered HDL cholesterol, elevated triglycerides, and elevated fasting glucose. Waist and hip size are not available in the CPRD. However the International Diabetes Federation suggests that if body mass index (BMI) is 30 kg/m^2 , central obesity can be assumed, thus we used this as a surrogate measure²⁷. Type 2 diabetes was used to indicate “elevated fasting glucose” and was assessed using the READ codes for diagnosis. High cholesterol, which is a composite of elevated triglycerides and elevated low-density lipoprotein (LDL) cholesterol, was used to indicate “elevated triglycerides”. HDL cholesterol was not specified in the CPRD data and thus lowered HDL cholesterol was not used in our definition of MetS. This approach is similar to analyses conducted in SEER-Medicare data, which also does not capture lowered HDL cholesterol¹⁸. A subject was considered exposed to either high cholesterol or hypertension if he or she received both a diagnostic READ code for the condition and a prescription for an appropriate medication. The date of the treatment was considered the first date of exposure. An individual was considered exposed to MetS at the first date on which three or more conditions were present within the individual’s exposure window of opportunity, explained further below.

Definition of Gastroesophageal reflux (GERD)

GERD-related READ codes for “heartburn”, “esophagitis”, “reflux”, “reflux and esophagitis”, and “peptic ulcer of the esophagus” were used to define GERD. In a sensitivity analysis, we restricted the analysis to subjects who received at least four prescriptions for anti-GERD medications (e.g., proton pump inhibitors [PPIs], H2 receptor antagonists [H2RAs]), regardless of documentation of a GERD-related READ code.

Definition of Exposure Period

We included a one-year exposure lag period that preceded the index date to limit differential ascertainment bias due to clinical work-up. All exposures and diagnoses were measured from the start of active patient history until the one-year exposure lag period prior to index date. Where controls entered the database earlier than their matched case, the case’s date of entry was used as the control’s exposure ascertainment start date.

Statistical Analyses

We provide patient characteristics calculated as frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Assessed variables included age, sex, exposure window (years of CPRD data included in analysis), Charlson comorbidity score (categorical: 0, 1, 2, 3+), number of GERD prescriptions, metabolic conditions (obesity, hypertension, high cholesterol, type 2 diabetes), and MetS. Conditional logistic regression models were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of associations between metabolic exposures and the outcomes of BE and EA²⁸. We also conducted multivariable logistic regression analyses stratified by presence of GERD and/or sex to assess effect-modification, since GERD may be associated with MetS and sex may modify the effect of obesity^{29, 30}. Covariates in these models included the main matching variables of age (quartiles), years of CPRD data included in analysis (quartiles), and sex (as appropriate). Other covariates (e.g. smoking, Charlson comorbidity score) did not alter the log odds ratio estimates for MetS by 10% and were not included in final models. To test for differences across strata, we used the likelihood-ratio statistic to compare nested models of the main-effect of MetS with a model that also included a MetS-GERD or a MetS-sex categorical interaction term. All analyses were performed using Stata software version 13. All statistical tests were two-sided and P-values less than 0.05 were considered to be statistically significant.

RESULTS

In total, 10,215 BE cases and 592 EA cases were included in our analysis (Table 1). A majority of BE cases (63%) and EA cases (80%) were male. BE and EA cases were more likely to have a history of GERD, compared with their matched controls. The proportion of each metabolic condition, except type 2 diabetes was slightly greater in both BE and EA cases compared with their matched population controls.

MetS was marginally associated with BE (OR: 1.12; 95%CI: 1.00–1.25; Table 2), as were obesity, hypertension, and high cholesterol. Unlike the BE analysis, MetS was not associated with EA (OR: 1.01; 95%CI: 0.65–1.56; Table 2). Obesity and hypertension were associated with EA, but high cholesterol and type 2 diabetes were not.

In BE models stratified by history of GERD, in the non-GERD stratum, MetS was associated with an OR of 1.33 (95%CI: 1.12–1.58) compared with people without MetS (Table 3). However, among those with a history of GERD, an inverse association between MetS and BE was observed (OR: 0.79, 95%CI: 0.68–0.91). The test for effect-modification by GERD was statistically significant ($P_{\text{effect-modification}} < 0.0001$). The individual metabolic conditions of hypertension (OR: 1.24, 95%CI: 1.15–1.34) and high cholesterol (OR: 1.23, 95%CI: 1.09–1.39) were modestly associated with risk of BE among patients without a history of GERD. We observed a positive linear trend in the magnitude of association with number of metabolic conditions and BE among those without a history of GERD, and an inverse linear trend with BE among those with a history of GERD (Supplemental Table 1). Further stratification by sex yielded no significant differences among those with no history of GERD ($P_{\text{effect-modification}} = 0.53$; Supplemental Table 2).

In contrast to BE models stratified by GERD, there remained no association between MetS and EA when stratified by GERD (Supplemental Table 3) or sex (Supplemental Table 4). Nor was there an increased risk with increasing number of metabolic conditions in relation to EA with or without GERD (Supplemental Table 1).

Discussion

In this large population-based analysis within the UK CPRD—which included 10,215 BE cases and 592 EA cases—we found that MetS was associated with a slightly elevated risk of BE compared with those without MetS. The individual components of MetS that contributed to this association were obesity, hypertension, and high cholesterol. GERD was found to be an effect-modifier of this association, whereby the positive associations were restricted to patients without GERD symptoms. Although we observed no association between MetS and EA, obesity and hypertension were associated with a slight increased risk of this malignancy.

We previously reported a positive association between MetS and BE in an older-aged US population (SEER-Medicare), which was present primarily in those without a prior history of GERD¹⁸. The results from this current study—in which we were able to assess the full age-range of patients and had improved capture of conditions that comprise MetS—are consistent with our prior study. We previously hypothesized that when direct pro-inflammatory effects of reflux do not predominate, systemic inflammation—represented by MetS—may increase the risk of BE. In addition, high cholesterol and hypertension were independently associated with risk of BE in the absence of GERD, even after adjusting for all other metabolic conditions. However, the magnitude of association was strongest for MetS as a combined entity among people without GERD. Together these results suggest that the disrupted metabolic state, represented by MetS, may confer the greatest risk for BE in the no GERD stratum.

Curiously, and unlike our prior SEER-Medicare study of BE¹⁸, the GERD-stratified analysis provided inverse associations between individual metabolic conditions of MetS and BE in those *with* a history of GERD. Although there is no obvious explanation for these inverse associations, there are some possible interpretations that warrant discussion. First, our result could be a chance observation given the number of tests conducted, although we do have a reasonably large case-control population and the analysis of number of metabolic conditions also supported an inverse association. Second, surveillance bias is one possible explanation. BE patients have less sensitivity than GERD patients for similar acid exposure^{31, 32}. One may posit that the GERD-population contained more patients with reflux symptoms unresponsive to PPIs, given the known desensitization of the esophagus in individuals with BE. These GERD patients without BE may have received more intensive medical work-up, which would have provided more opportunity for diagnosis of metabolic conditions.³¹ Third, it is possible that *treating* the individual metabolic conditions of MetS could decrease systemic inflammation. There is some evidence that regular statin use, primarily used to treat high cholesterol, can decrease risk of BE.³³ Future research investigating the association of MetS and BE should consider assessing whether statin medications affect these relationships.

We did not observe a positive association between MetS and EA regardless of history of GERD. This is in contrast to our recent SEER-Medicare study in which we observed a positive association between MetS and EA² as well as a recent study that reported increasing risk of EA with increasing metabolic dysfunction¹⁹. Differences in the underlying populations (e.g. greater propensity for MetS-related conditions) and/or medical practice patterns (e.g. medication management of high-risk pre-diabetic patients) might explain the divergent results. Notably the difference in diabetes prevalence is striking — 26% of population controls in SEER-Medicare versus 9% of population controls in CPRD (when restricted to ages 65.5 years or older). The low prevalence of diabetes limited the number of individuals exposed to MetS, which may have contributed to the null association between MetS and EA. The total number of EA cases was much smaller in the CPRD (n=592) compared with SEER-Medicare (n=5,264), yielding lower power to detect an association with MetS. Further investigation is needed to determine whether MetS increases risk of EA beyond the deleterious effects of obesity alone.

Definitions of MetS, including the one used in this study, are based on assigning a condition as present or absent, however the relevance of this methodology is questionable since MetS is not a dichotomous state. MetS exists as a gradient of inflammation severity that is based on the magnitude of alteration from normal metabolic levels. To that end—as well as for purposes of exposure harmonization across cohorts—a recent study derived a continuous metabolic risk score and demonstrated positive associations between increasing metabolic score and risk of numerous cancers, including EA^{19, 20}. Akin to the MetS risk score²⁰ and consistent with the study by Thrift *et al.*²¹, we did observe increasing risk of BE with increasing number of metabolic conditions in those without GERD, however, we did not observe this pattern in relation to EA (Supplemental Table 1). Neither study reported GERD stratified analyses. Nevertheless, our data suggests that MetS may be an indirect pathway by which obesity increases risk of BE, but not of EA.

The strengths of this study include the population-based ascertainment of the study population, providing wide generalizability. This study was not subject to some usual limitations of retrospective case-controls studies—selection bias was minimized since our cases and controls were drawn from the same baseline population and prospective electronic capture of diagnosis and treatments avoided recall bias. Our population was also sufficient in size to enable stratification by GERD and sex. Our study also has certain limitations. Firstly, although there is precedent for using READ codes to identify BE patients in CPRD³⁴⁻³⁶ we do not have direct access to pathology reports and cannot offer an independent confirmation. Nevertheless, non-differential misclassification would usually bias the results towards the null. When we conducted a sensitivity analysis in which we restricted BE cases to those with at least two READ codes for BE, MetS was associated with a 59% increased risk (OR: 1.59, 95%CI 1.15–2.07) compared with the 12% observed in our main analysis (Supplemental Table 5). Secondly, although identification of metabolic conditions based on READ codes has high validity for chronic conditions^{22, 23} and avoids recall bias in self-reported measures, our results suggest that exposure is clinically under-ascertained. Our clinical prevalence estimate of MetS at 3–4% is low compared with other estimates of MetS prevalence³⁷. Physician and/or laboratory values would provide a more precise evaluation of MetS. Thirdly, we did not have NSAID or statin medication usage in our dataset which

have previously been associated with Barrett's esophagus and could potentially interact with the association of metabolic syndrome and Barrett's esophagus. Lastly, a GERD diagnosis usually requires symptoms and thus primarily captures symptomatic reflux. To maximize sensitivity, we defined GERD as the presence of a single READ code of a GERD-related condition. Using more conservative definitions to determine history of GERD (e.g. requiring multiple READ codes or multiple prescriptions) did not substantively change the effect estimates or effect modification observed (Supplemental Table 6).

This is the largest population-based study to date that provides evidence of a modest association between MetS and BE. Our findings suggest that a systemic inflammatory state, represented by MetS, could slightly elevate the risk for BE and represent a GERD-independent casual pathway. Whether MetS has an etiologic role in development of EA remains unclear.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by the Intramural Program of the National Cancer Institute at the National Institutes of Health and Department of Health and Human Services.

Abbreviations

BE	Barrett's esophagus
CPRD	Clinical Practice Research Datalink
EA	esophageal adenocarcinoma
GERD	gastroesophageal reflux disease
MetS	metabolic syndrome

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Novelty and Impact

This is the largest population-based study to date that provides evidence of a modest association between MetS and BE. Our findings suggest that a systemic inflammatory state, represented by MetS, could increase risk for BE and represent a GERD-independent casual pathway. No association between MetS and risk of EA was detected. Whether MetS has an etiologic role in development of EA remains unclear.

Highlights

- Metabolic syndrome (MetS) increased risk of Barrett's esophagus (BE)
- GERD modified the association with increased risk confined to those without reflux
- No association between MetS and risk of EA was detected
- MetS may represent a reflux-independent inflammatory pathway that increases BE risk

Table 1

Characteristics of study population

Variable	BE cases N= 10,215		Population controls N= 50,167		EA cases N= 592		Population controls N= 2,901	
	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)
Mean age (SD) [†]	64.0 (13.9)	63.7 (13.7)	69.2 (11.3)	68.9 (11.2)				
Male sex [†]	62.6% (6,399)	62.5% (31,375)	80.1% (474)	79.9% (2,319)				
History in CPRD [†]								
2–5 yrs.	14.3% (1,463)	14.5% (7,258)	15.2% (90)	15.4% (446)				
>5–10 yrs.	31.6% (3,227)	31.8% (15,932)	26.4% (156)	26.2% (761)				
>10–15 yrs.	33.9% (3,463)	33.8% (16,978)	34.5% (204)	34.5% (1,000)				
>15 yrs.	20.2% (2,062)	19.9% (9,999)	24.0% (142)	23.9% (694)				
Charlson comorbidity score								
None (0)	66.2% (6,764)	73.4% (36,832)	59.3% (351)	67.6% (1,960)				
Low (1)	23.9% (2,442)	18.9% (9,458)	26.5% (157)	21.7% (629)				
Moderate (2)	6.5% (664)	5.3% (2,665)	9.6% (57)	7.4% (216)				
High (3+)	3.4% (345)	2.4% (1,212)	4.6% (27)	3.3% (96)				
Smoking status								
Never	38.5% (3,937)	37.3% (18,718)	31.6% (187)	35.7% (1,036)				
Former	28.6% (2,918)	24.7% (12,388)	36.1% (214)	32.3% (936)				
Current	16.4% (1,671)	16.2% (8,148)	21.3% (126)	15.2% (441)				
Unknown	16.5% (1,689)	21.8% (10,913)	11.0% (65)	16.8% (488)				
History of GERD	57.8% (5,902)	25.0% (12,535)	53.0% (314)	28.6% (829)				
Number of GERD prescriptions								
0	38.6% (3,947)	69.1% (34,675)	45.1% (267)	64.7% (1,876)				
1–3	13.5% (1,376)	10.8% (5,408)	7.1% (42)	12.2% (355)				
4–6	8.0% (816)	4.5% (2,247)	3.7% (22)	4.6% (134)				
7–24	16.1% (1,641)	6.9% (3,456)	11.8% (70)	8.0% (232)				
25–36	6.5% (665)	2.2% (1,094)	6.1% (36)	2.9% (83)				
37+	17.3% (1,770)	6.6% (3,287)	26.2% (155)	7.6% (221)				

Variable	BE cases N= 10,215	Population controls N= 50,167	EA cases N= 592	Population controls N= 2,901
	% (N)	% (N)	% (N)	% (N)
Metabolic conditions				
Obesity (BMI ≥ 30)	20.7% (2,114)	19.2% (9,607)	24.7% (146)	20.2% (585)
High cholesterol	9.5% (974)	8.5% (4273)	11.1% (66)	10.3% (300)
Hypertension	25.3% (2582)	23.1% (11569)	31.6% (187)	27.3% (793)
Type 2 diabetes	6.0% (609)	5.6% (2789)	7.4% (44)	7.3% (212)
Metabolic syndrome	4.0% (410)	3.6% (1814)	4.4% (26)	4.4% (127)

Abbreviations: BE, Barrett’s esophagus; EA, esophageal adenocarcinoma; BMI, body mass index; GERD, gastroesophageal reflux disease; SD, standard deviation; yrs., years.

/ Matching factors

Table 2
Association between metabolic syndrome and Barrett's esophagus and esophageal adenocarcinoma

Exposure	BE vs Population controls				EA vs Population controls			
	BE cases N= 10,215		Population controls N= 50,167		EA cases N= 592		Population controls N= 2,901	
	% (N)		% (N)		% (N)		% (N)	
Metabolic syndrome	4.0% (410)	3.6% (1,814)	1.12 (1.00,1.25)	0.057	4.4% (26)	4.4% (127)	1.01 (0.65,1.56)	0.976
Metabolic conditions								
Obesity (BMI ≥ 30)	20.7% (2,114)	19.2% (9,607)	1.11 (1.05,1.17)	<0.001	24.7% (146)	20.2% (585)	1.31 (1.06,1.62)	0.014
Hypertension	25.3% (2,582)	23.1% (11,569)	1.13 (1.07,1.20)	<0.001	31.6% (187)	27.3% (793)	1.25 (1.01,1.53)	0.036
High cholesterol	9.5% (974)	8.5% (4,273)	1.15 (1.06,1.24)	0.001	11.1% (66)	10.3% (300)	1.10 (0.82,1.49)	0.513
Type 2 diabetes	6.0% (609)	5.6% (2,789)	1.07 (0.98,1.18)	0.143	7.4% (44)	7.3% (212)	1.04 (0.73,1.47)	0.835

Abbreviations: BE, Barrett's esophagus; EA, esophageal adenocarcinoma; BMI, body mass index; OR, odds ratio; CI, confidence interval.

[/] All models were conditioned on age, years of CPRD data prior to selection, and sex.

Table 3

Association between metabolic syndrome and Barrett's esophagus, stratified by history of gastroesophageal reflux disease

Exposure	No GERD				GERD			
	BE cases N= 4,313	Population controls N= 37,632	% (N)	P Value	BE cases N= 5,902	Population controls N= 12,535	% (N)	P Value
Metabolic syndrome	3.7% (158)	2.7% (1027)		0.001	4.3% (252)	6.3% (787)		0.001
<i>p-value of GERD effect modification</i>								
<i>P<0.0001</i>								
Metabolic conditions								
Obesity (BMI ≥30)	17.9% (772)	17.0% (6410)		0.132	22.7% (1342)	25.5% (3197)		0.001
Hypertension	24.5% (1058)	20.1% (7555)		<0.001	25.8% (1524)	32.0% (4014)		0.002
High cholesterol	8.1% (349)	6.5% (2444)		0.001	10.6% (625)	14.6% (1829)		<0.001
Type 2 diabetes	5.3% (230)	4.7% (1768)		0.193	6.4% (379)	8.1% (1021)		0.071

Abbreviations: BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; BMI, body mass index; OR, odds ratio; CI, confidence interval.

[†] All models were adjusted for age quartiles, years of CPRD data prior to selection, and sex.