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Metabolic syndrome and risk of esophageal adenocarcinoma in the United States elderly: An analysis of SEER-Medicare data

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Abstract

Background—Metabolic syndrome (MetS) is associated with cancer risk and increases the risk of Barrett's esophagus, the precursor lesion of esophageal adenocarcinoma (EA), primarily in the absence of gastroesophageal reflux disease (GERD). However, little is known about whether MetS is associated with risk of EA.

Methods—Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database we evaluated whether MetS was associated with EA. EA cases (n=3,167) were compared with individually matched population controls (5:1); a subset of EA cases (n=575) were able to be individually matched to Barrett's esophagus controls (n=575). MetS was defined using ICD-9-CM codes in the period 1–3 years prior to EA diagnosis or control selection. Unconditional logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). Potential effect-modification by GERD symptoms and sex was examined in stratified models.

Results—EA was significantly associated with MetS (OR: 1.16, 95%CI: 1.06, 1.26) compared with population controls. In males, the association was restricted to those without prior GERD, however in females MetS was associated with EA regardless of GERD status. Effect modification by sex was observed (p-interaction=0.01). MetS was not associated with EA risk when compared with Barrett's esophagus controls.

Conclusions—In this older population, MetS was associated with an increased risk of EA in males without GERD and females regardless of GERD status. Given the lack of an association when compared with Barrett's esophagus controls, MetS may impact EA risk by primarily increasing risk of the precursor lesion Barrett's esophagus.

Condensed abstract

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MetS was associated with an increased risk of EA in males without GERD and females regardless of GERD status in the SEER-Medicare linked database. MetS may impact EA risk by primarily increasing risk of the precursor lesion Barrett's esophagus.

Keywords

Barrett Esophagus; Risk Factors; Esophageal Cancer; Gastroesophageal Reflux; Obesity

INTRODUCTION

The incidence of esophageal adenocarcinoma (EA) has rapidly increased in the U.S. over the last three decades [1]. EA is a lethal malignancy with a majority of cases surviving less than one year [2]. This malignancy is thought to arise within Barrett's esophagus (BE), a metaplasia caused by chronic exposure to gastroesophageal reflux [3]. Previous studies have demonstrated that obesity increases the risk of gastroesophageal reflux disease (GERD) [4, 5], although the mechanisms by which obesity promotes EA development are not completely understood and are likely multifactorial [6].

Obesity, especially central adiposity, can increase risk of GERD by amplifying intra-gastric pressure [7], disrupting normal esophageal sphincter function [8], and increasing risk of hiatus hernia [9]. However, in addition to the impact of these "mechanical" sequelae of obesity, obesity may increase the risk of EA and BE by a route that is independent of GERD. One such mechanism may include promoting inflammation by secreting multiple proinflammatory cytokines (e.g. tumor necrosis factor-α, interleukin-6, leptin, adiponectin, [10]). A proxy for such obesogenic effects is metabolic syndrome (MetS) [11], which is defined as a constellation of metabolic disorders that include obesity, impaired fasting glucose, high blood pressure, and dyslipidemia. MetS has been associated with increased risks of cardiovascular disease, total mortality [12], and various malignancies [13, 14].

In a prior study of SEER-Medicare data we have shown that MetS was associated with increased risk of BE, the precursor lesion of EA. However the association was restricted to those without a history of GERD [15]. We proposed that the direct, proinflammatory effects of GERD cause esophageal tissues to reach a saturated inflammatory state, in which the effects of MetS have little or no additional effect, negating any observable association. Conversely, in those without symptomatic GERD, systemic inflammation conferred by MetS increases risk of BE.

Although a few studies have demonstrated that BE is associated with MetS [15–18], only a single study has evaluated MetS in relation to EA using multiple prospective cohorts with accrual of 114 EA cases in total [19]. MetS was associated with an increased risk of EA. Considering that obesity was the only metabolic factor associated with EA, the authors concluded that the association was likely attributable to obesity increasing the propensity for GERD. However, given that MetS has previously been associated with BE in those without a history of GERD, evaluating MetS in relation to EA by reflux exposure is warranted. Furthermore, MetS could increase risk of EA by increasing the risk of the precursor lesion, BE, or by increasing risk of BE progression to cancer. Therefore, we assessed whether MetS

—as a proxy of systemic inflammation—was associated with EA risk overall and in sub-groups defined by GERD and sex in an analysis of the SEER-Medicare database.

METHODS

Data Source

For this study we used the SEER-Medicare database, which links cancer registry data from SEER and Medicare enrollment and health claims files. The population-based SEER registries collect demographic and clinical information for each patient living in defined geographic areas. The SEER areas included in our study cover approximately 28% of the U.S. population. The Medicare data, collected by the Center for Medicare and Medicaid Services (CMS), include claims for each beneficiary with fee-for-service coverage, with information about all inpatient hospitalizations, outpatient and physician services. All files include dates of service and codes for diagnoses and procedures using the International Classification of Disease, ninth revision (ICD-9-CM) codes. The database is comprised of multiple files that were created during an electronic linkage of the SEER and Medicare data, as has been previously described [20, 21]. The SEER-Medicare files were used to identify EA cases and two control groups–population controls (Medicare beneficiaries) and BE controls (described further below).

Study Population

We identified all individuals diagnosed with EA in the SEER-18 registries during 2003–2009 with ICD-9: 150.0–150.9; ICD–O: 8140–8575. Cases diagnosed at autopsy or death certificate were excluded.

To ensure complete Medicare coverage for each individual, those not enrolled in Medicare Parts A and B continuously for at least 3 years before diagnosis/selection were excluded. We further excluded those enrolled in Medicare before age 64.5 years, and enrollment in an HMO (Health Maintenance Organization). Given inclusion criteria EA cases and controls were ≥67.5 years at diagnosis/ selection.

We selected two control groups from the 5% random sample of Medicare beneficiaries residing in SEER regions—population controls and BE controls based on incidence-density sampling with replacement between risk-sets. Five population controls were selected for each EA case diagnosed 2003–2009 based on age at diagnosis (+/−1 year), sex, race, and SEER registry. Population controls were those who by July 1st of the calendar year of diagnosis of the corresponding case had not had an EA diagnosis. Complete matching resulted in inclusion of 3,167 EA cases and 15,835 population controls.

To the extent possible, one BE control was selected for each EA case diagnosed 2003–2009 using the same matching variables as the population controls. BE controls were defined as Medicare beneficiaries with a BE diagnosis after July 1, 2003 through 2009. The BE diagnosis was captured by ICD-9-CM code 530.85 which is a code specific for BE that was introduced by CMS in 2003. In addition, we required the BE controls to have undergone an endoscopy (43200, 43201–43205, 43215–43217, 43219, 43220, 43226–43228, 43231, 43232, 43234–43251, 43255–43259) within the period three months prior-to one month

post-date of BE diagnosis. BE controls identified with ICD-9-CM code 530.85 were excluded if they had a prior diagnosis with ICD-9-CM 530.2 (ulcer of the esophagus) which has previously been used for BE but is non-specific. The Barrett's control pool was limited by matching on month and year of diagnosis and by SEER registry. Only a subset of EA cases could be matched with a BE control. Incomplete matching in the EA compared with BE analysis resulted in inclusion of 575 EA cases and 575 BE controls.

Definition of Metabolic Syndrome and Covariate Selection

MetS was defined as suggested by the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [22] which requires the presence of at least three of the following conditions: elevated waist circumference/central obesity, elevated triglycerides, lowered high-density lipoprotein cholesterol, high blood pressure, and elevated fasting glucose. There was no specific ICD-9-CM code for elevated waist circumference prior to 2001, therefore we used an indication of obesity or morbid obesity as a proxy for this exposure. Reduced high-density lipoprotein cholesterol was not assessed due to the absence of a specific ICD-9-CM code for this condition. Type II diabetes diagnoses were included in the definition of elevated fasting glucose. This definition of MetS in studies of SEER-Medicare data has been used previously [15, 23]; it includes the following ICD-9-CM codes: obesity: 278.0, 278.01, 278.00, V85.3, V85.4; elevated triglycerides: 272.0, 272.1, 272.2, 272.4, 272.5, 272.9; high blood pressure/hypertension: 401, 401.0, 401.1, 401.9, 402, 402.0, 402.1, 402.9, 403, 403.0, 403.1, 403.9, 404, 404.0, 404.1, 404.9; elevated fasting glucose/ type II diabetes mellitus: 250, 790.2, 790.21, 790.22, 790.29 [24].

We also included the following risk factors previously demonstrated to be associated with EA: tobacco smoking (yes/no), defined using codes for personal history of tobacco use, excessive use of tobacco products and toxic effect of tobacco (V15.82, 305.1, 989.84); and GERD symptoms (yes/no), defined using codes for gastroesophageal reflux, reflux esophagitis, esophagitis, or heartburn (530.81, 530.11 530.10, 787.1). Risk factors, including metabolic factors, were identified between one and three years prior to either EA diagnosis or index date for population controls. We excluded conditions documented in the year preceding the diagnosis date or index date to reduce differential ascertainment bias that may result from increased medical encounters in the year prior to cancer diagnosis.

Modified Charlson Comorbidity Score

We derived a comorbidity score for each individual based on the clinical comorbidity index [25] developed by Charlson [26], updated by Deyo [27] and expanded by Klabunde et al [28]. Briefly, our Charlson comorbidity score was a weighted-score based on inpatient and outpatient Medicare claims data during the exposure window of three years to one year prior to cancer diagnosis, BE diagnosis, or pseudo-diagnosis date. The Charlson comorbidity weighted-score was categorized into none (0), low (1), moderate (2), and high (3+).

Statistical Analyses

To characterize the case and control groups, we calculated frequencies and percentages for categorical variables and the means and standard deviations for continuous variables. Assessed variables included age at diagnosis or selection (continuous), sex, race (white,

black, other/unknown), SEER registry, Charlson comorbidity score (categorical: 0, 1, 2, 3+), GERD (yes/no), type II diabetes, individual metabolic conditions (obesity, elevated fasting glucose, elevated blood pressure, elevated triglycerides), and MetS.

Unconditional logistic regression models were used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) of associations between MetS exposures and EA [29]. The models included variables whose inclusion altered the log odds ratio estimates for MetS by >10% (smoking), factors with a known or probable association with EA (GERD), and the matching variables (age, sex, race, and SEER registry) [30]. Additional adjustment for the severity of comorbidities as captured by the Charlson comorbidity index score did not change effect estimates and therefore were not included in the final adjusted models. We assessed effect-modification by including an interaction term of GERD and MetS in adjusted logistic regression models and examining the Wald p-value for interaction, as well as through analyses stratified by GERD and by sex, since GERD may be associated with MetS [31–33] and sex plays pivotal roles in the development of MetS and EA. A two-sided P-value of <0.05 was considered statistically significant. All analyses were performed using Stata software version 13.

RESULTS

Table 1 shows selected characteristics of the two case-control groups that were selected. The majority of EA cases diagnosed 2003–2009 were white and male. The prevalence of smoking was higher in the EA cases (11.4%) compared with population controls (7.7%), but similar to that in BE controls (each 12%). EA cases had a greater proportion of gastroesophageal reflux (26.1%) compared with population controls (18.0%), but less compared with BE controls (27.1% vs. 38.8%, respectively).

Table 2 summarizes the associations of EA with MetS and individual conditions of MetS. EA cases were significantly more likely to have had MetS compared with population controls (OR: 1.16, 95%CI: 1.06, 1.26; P=0.001). Of the individual components, obesity, elevated fasting glucose, and high blood pressure were each significantly associated with increased risk of EA in individual models. There was no association between MetS and EA risk when cases were compared with BE controls (OR: 1.01, 95%CI: 0.78, 1.31; P=0.94). Additionally, no individual component of MetS was significantly associated with increased EA risk. Obesity appeared to be positively associated with EA risk (OR: 1.45, 95%CI: 0.88, 2.40) compared with BE controls, however the association did not reach statistical significance (P=0.143). A nominally statistically significant inverse association was observed between elevated triglycerides and EA when compared with BE (OR: 0.75, 95%CI: 0.57, 0.99; P=0.042).

Table 3 summarizes the association of EA with MetS and individual conditions of MetS stratified by GERD status. In the no-GERD stratum, MetS was associated with an OR of 1.19 (95%CI: 1.08, 1.32) comparing EA cases with population controls. (Table 3). Among those with a history of GERD, however, no significant association between MetS and EA was observed (OR: 1.07, 95% CI: 0.90, 1.27) and the Wald p-value for interaction was not statistically significant ($P_{\text{-interaction of GERD}}$ =0.231). Additional stratification by sex

provided tentative evidence for stronger associations in females (ORs~1.4) that, unlike the more attenuated results for males, did not appear to differ by GERD status (Table 4). When stratified by sex alone, the association of MetS and EA appeared stronger in females (OR: 1.44, 95% CI: 1.20, 1.73) than in males (OR: 1.09, 95% CI: 0.99, 1.20; $P\text{-}_{interaction}$ =0.011) (Supplemental Table 1).

DISCUSSION

In this large population-based analysis, we report a positive association between MetS and the risk of EA when compared with population controls. This association appeared stronger in those without a prior history of GERD, although this difference was not statistically significant. There was tentative evidence that the overall association between MetS and EA was stronger in women than men. There was no evidence of effect-modification by GERD in women, but modest evidence in men. There was no association between MetS and EA when compared with BE controls. This study is the first population-based study to evaluate the association of MetS and EA risk in the U.S..

MetS and GERD both represent proinflammatory states. Although local inflammation induced by reflux may be the dominant mechanism by which cytokines, reactive oxygen species and other factors are released– leading to a proinflammatory and favorable tumor microenvironment– this does not preclude a role for systemic inflammation that may be captured by MetS [6]. Our results suggest that, in men, when direct inflammatory routes of association are not saturated by the inflammatory effects of GERD, an indirect proinflammatory state may contribute to risk of EA. Why the association of MetS and EA may be stronger in women and may not differ by GERD is unknown. Interestingly, women presenting with GERD are more likely to have non-erosive disease (i.e. reflux symptoms and a normal endoscopy), whereas men are more likely to have erosive esophagitis [34, 35]. This could be related to the observation that testosterone is positively associated with BE [36], possibly due to inhibition of re-epithelization [37–39] which could expand the interval for opportunistic metaplastic re-population and subsequent malignancy. Alternatively, sex differences in anti-oxidative capacity [40] may equip women with a more favorable response to the direct, inflammatory effect of GERD, enabling indirect, systemic inflammation to contribute to disease risk regardless of GERD status. This idea is consistent with rat reflux esophagitis model experiments that have shown esophageal tissue damage [41] and inflammation [42] to be more severe in males compared with females.

Healthcare seeking behaviors may also explain some of our observations. Women report significantly higher symptom severity scores for heartburn and regurgitation compared with men of the same GERD stage [34], which could imply that women would seek more medical attention, receive more thorough medical work-up and have more opportunity for diagnosis of the components of MetS compared with men. Although if the perceived sex difference is attributed to increased healthcare utilization by women, then it is possible that men with MetS are also at increased risk of EA, regardless of GERD status.

The main result from this study of a positive association between MetS and EA is consistent with the only prior study to assess this hypothesis [19]. However, this prior study did not

present results stratified by GERD. In addition to demonstrating that MetS increases risk of EA, it is also of interest to the field whether the association is driven by increasing the risk of the precursor lesion, BE, or by increasing risk of BE progression to cancer. No studies have directly addressed the issue, however, a review hypothesized that MetS may be a risk factor for carcinogenic progression of BE [6]. Although we were unable to directly assess such, we did evaluate the association of MetS and EA compared with BE controls and found no association. BE tissue is known to express an array of proinflammatory cytokines including IL-6 (24), IL-8 (22), IL-1β, and IL-10 (21). Furthermore the severity of BE dysplasia is also associated with greater expression of proinflammatory cytokines including the transcription factor NF-κB (22). Given the proinflammatory microenvironment that typifies BE, it seems unlikely that systemic inflammation—represented by MetS—could further increase risk of EA. Indeed, our results support a mechanism by which MetS increases risk of EA possibly through increasing risk of BE [15] and not by increasing the carcinogenic progression of BE.

Although the SEER-Medicare data enabled us to conduct a large study to test our hypotheses, several limitations inherent to the data constrain the interpretation and generalizability of our results. Our findings are restricted to U.S. adults aged ≥ 67.5 years and older. Our definition of MetS relied on medical billing, which insufficiently captured several exposure conditions, thus under-estimating the number exposed to MetS in this population. We also observed low prevalence of obesity and smoking; however, capture efficiency is unlikely to differ by group and therefore should not bias our results. Due to the low sensitivity of GERD symptoms for acid reflux, misclassification could have occurred but this would usually bias results towards the null. In addition, GERD symptoms are highly specific and have been shown to correlate with severity of exposure [43].

The strengths of this study include the population-based ascertainment of cancer cases from cancer registries and Medicare beneficiaries randomly selected from within SEER cancer registry catchment areas. We were able to evaluate the presence of MetS prior to EA diagnosis. Our population was also large enough to allow analysis stratified by GERD and sex.

Using administrative data, a cost-effective approach to study risk factors of cancer, we are the first to demonstrate that MetS is associated with an increased risk of EA in men in the absence of GERD and women regardless of GERD status in an older population. We propose that systemic inflammation conferred by MetS increases risk of EA primarily by increasing the risk of the precursor lesion BE. Future studies should evaluate if treating the conditions of metabolic syndrome decreases risk of BE and EA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of study population selected from SEER-Medicare, 2003–2009

	EA cases N= 3,167		Population controls N= 15,835		EA cases N= 575		BE controls N= 575	
Variable	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Mean age (SD)[1]	78.0 (6.5)		78.0 (6.5)		76.6 (5.4)		76.7 (5.5)	
Male sex[1]	2,481	78.3%	12,405	78.3%	435	75.7%	435	75.7%
Race[1]								
White	3,036	95.9%	15,180	95.9%	>553	96.0%	>553	96.0%
Black	55	1.7%	227	1.7%	<11	<2.0%	<11	<2.0%
Unknown/other	76	2.4%	380	2.4%	<11	<2.0%	<11	<2.0%
Charlson comorbidity score								
None (0)	1,942	61.3%	10,643	67.2%	350	60.9%	349	60.7%
Low (1)	698	22.0%	2,964	18.7%	135	23.5%	123	21.4%
Moderate (2)	295	9.3%	1,282	8.1%	48	8.3%	63	11.0%
High (3+)	234	7.4%	946	6.0%	42	7.3%	40	7.0%
Medicaid dual enrollment	220	7.0%	1,606	10.1%	32	5.6%	43	7.5%
Smoking	362	11.4%	1,223	7.7%	70	12.2%	69	12.0%
Gastroesophageal reflux	828	26.1%	2,844	18.0%	156	27.1%	223	38.8%
Metabolic conditions								
Obesity	172	5.4%	625	4.0%	40	7.0%	29	5.0%
Elevated glucose	1,028	32.5%	4,654	29.4%	191	33.2%	181	31.5%
Elevated blood pressure	2,335	73.7%	11,147	70.4%	434	75.5%	459	79.8%
Elevated triglycerides	2,114	66.8%	10,502	66.3%	409	71.1%	444	77.2%
MetS (overall)[2]	870	27.5%	3,800	24.0%	171	29.7%	169	29.4%

Abbreviations: EA, esophageal adenocarcinoma; BE, Barrett's esophagus; MetS, metabolic syndrome.

[1] Matching factors

[2] NCEP-ATP III definition

Table 2

Association between metabolic syndrome and esophageal adenocarcinoma compared with population controls and Barrett's esophagus controls

	EA vs. Population controls (2003–2009)						EA vs. BE controls (2003–2009)					
	EA cases N= 3,167		Population controls N= 15,835				EA cases[1] N= 575		BE controls N= 575			
Exposure	**N**	**%**	**N**	**%**	**OR (95% CI)[2]**	***P* Value**	**N**	**%**	**N**	**%**	**OR (95% CI)[2]**	***P* Value**
MetS[3]	870	27.5	3,800	24	1.16 (1.06, 1.26)	0.001	171	29.7	169	29.4	1.01 (0.78, 1.31)	0.940
Metabolic conditions												
Obesity	172	5.4	625	3.9	1.32 (1.10, 1.57)	0.002	40	7	29	5.0	1.45 (0.88, 2.40)	0.143
Elevated fasting glucose	1,028	32.5	4,654	29.4	1.12 (1.03, 1.22)	0.006	191	33.2	181	31.5	1.09 (0.84, 1.40)	0.523
High blood pressure	2,335	73.7	11,147	70.4	1.10 (1.00, 1.20)	0.046	434	75.5	459	79.8	0.81 (0.60, 1.08)	0.147
Elevated triglycerides	2,114	66.8	10,502	66.3	0.95 (0.88, 1.04)	0.276	409	71.1	444	77.2	0.75 (0.57, 0.99)	0.042
Number of conditions												
1+	2,679	84.6	13,151	83.1	1.01 (0.91, 1.13)	0.846	495	86.1	522	90.8	0.69 (0.47, 1.00)	0.053
2+	2,019	63.8	9,731	61.5	1.03 (0.95, 1.12)	0.444	388	67.5	407	70.8	0.89 (0.68, 1.15)	0.376
3+	869	27.4	3,760	23.7	1.17 (1.07, 1.28)	<0.001	171	29.7	169	29.4	1.01 (0.78, 1.31)	0.940
4	82	2.6	286	1.8	1.34 (1.04, 1.73)	0.022	20	3.5	15	2.6	1.40 (0.69, 2.82)	0.349

Abbreviations: EA, esophageal adenocarcinoma; BE, Barrett's esophagus; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval.

[1] EA cases (n=575) are a subset of EA cases in EA vs. Population controls analysis

[2] All models were adjusted for age, sex, race, registry, smoking, history of GERD

[3] NCEP-ATP III definition

Table 3

Association between MetS and EA compared with population controls, stratified by gastroesophageal reflux status

	No GERD						GERD					
	EA cases N= 2,339		**Population controls N= 12,991**				**EA cases N= 828**		**Population controls N= 2,844**			
Exposure	**N**	**%**	**N**	**%**	**OR (95% CI)[2]**	***P* Value**	**N**	**%**	**N**	**%**	**OR (95% CI)[2]**	***P* Value**
MetS[1]	614	26.3	2,959	22.8	1.19 (1.08, 1.32)	0.001	256	30.9	841	29.6	1.07 (0.90, 1.27)	0.455
p-value of effect modification						*P=0.231*						
Metabolic conditions												
Obesity	116	5	460	3.5	1.39 (1.13, 1.72)	0.002	56	6.8	165	5.8	1.17 (0.85, 1.61)	0.331
Elevated fasting glucose	734	31.4	3,687	28.4	1.14 (1.04, 1.26)	0.006	294	35.5	967	34	1.07 (0.91, 1.26)	0.426
High blood pressure	1,648	70.5	8,782	67.6	1.12 (1.02, 1.24)	0.020	687	83	2,365	83.2	0.98 (0.79, 1.21)	0.864
Elevated triglycerides	1,495	63.9	8,274	63.7	1.00 (0.91, 1.10)	0.968	619	74.8	2,228	78.3	0.81 (0.67, 0.97)	0.023
Number of conditions												
1+	1,899	81.2	10,470	80.6	1.02 (0.91, 1.14)	0.749	780	94.2	2,681	94.3	0.98 (0.70, 1.38)	0.902
2+	1,427	61	7,604	58.5	1.09 (1.00, 1.20)	0.056	592	71.5	2,127	74.8	0.83 (0.70, 0.99)	0.043
3+	613	26.2	2,925	22.5	1.21 (1.09, 1.34)	<0.001	256	30.9	835	29.4	1.08 (0.91, 1.28)	0.382
4	54	2.3	204	1.6	1.44 (1.06, 1.95)	0.020	28	3.4	82	2.9	1.19 (0.76, 1.85)	0.448

Abbreviations: EA, esophageal adenocarcinoma; BE, Barrett's esophagus; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval.

[1] NCEP-ATP III definition

[2] All models were adjusted for age, sex, race, registry, smoking

Table 4

Association between MetS and EA compared with population controls, stratified by gastroesophageal reflux status and sex

	MALES						FEMALES					
NO GERD	EA cases N= 1,855		Population controls N= 10,296				EA cases N= 484		Population controls N= 2,695			
Exposure	N	%	N	%	OR (95% CI)[2]	*P* Value	N	%	N	%	OR (95% CI)[2]	*P* Value
MetS[1]	478	25.8	2,374	23.1	1.15 (1.02, 1.29)	0.020	136	28.1	585	21.7	1.42 (1.14, 1.77)	0.002
Metabolic conditions												
Obesity	93	5	362	3.5	1.42 (1.12, 1.80)	0.003	23	4.8	98	3.6	1.28 (0.79, 2.06)	0.311
Elevated fasting glucose	580	31.3	2,976	28.9	1.11 (1.00, 1.24)	0.056	154	31.8	711	26.4	1.31 (1.06, 1.62)	0.014
High blood pressure	1,270	68.5	6,782	65.9	1.11 (1.00, 1.24)	0.060	378	78.1	2,000	74.2	1.21 (0.95, 1.54)	0.116
Elevated triglycerides	1,178	63.5	6,579	63.9	0.97 (0.88, 1.08)	0.595	317	65.5	1,695	62.9	1.12 (0.91, 1.37)	0.295
GERD	EA cases N= 626		Population controls N= 2,109				EA cases N= 202		Population controls N= 735			
Exposure	N	%	N	%	OR (95% CI)[2]	*P* Value	N	%	N	%	OR (95% CI)[2]	*P* Value
MetS[1]	182	29.1	634	30.1	0.94 (0.77, 1.15)	0.570	74	36.6	207	28.2	1.52 (1.08, 2.14)	0.016
Metabolic conditions												
Obesity	39	6.2	116	5.5	1.14 (0.78, 1.68)	0.494	17	8.4	49	6.7	1.31 (0.72, 2.37)	0.379
Elevated fasting glucose	216	34.5	746	35.4	0.95 (0.79, 1.15)	0.616	78	38.6	221	30.1	1.51 (1.08, 2.11)	0.016
High blood pressure	507	81	1,735	82.3	0.90 (0.71, 1.14)	0.398	180	89.1	630	85.7	1.32 (0.79, 2.20)	0.283
Elevated triglycerides	473	75.6	1,673	79.3	0.79 (0.64, 0.99)	0.039	146	72.3	555	75.5	0.85 (0.58, 1.25)	0.416

Abbreviations: EA, esophageal adenocarcinoma; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval.

[1] NCEP-ATP III definition

[2] All models were adjusted for age, race, registry, smoking.