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This is a Peer Reviewed Accepted version of the following article, accepted for publication in *Cancer Causes and Control*.

2016-12-20

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Cancer Causes Control. 2015 Dec;26(12):1825-34.

<http://doi.org/10.1007/s10552-015-0675-4>

<http://hdl.handle.net/10616/45458>

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Metabolic Syndrome and Esophageal and Gastric Cancer

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Keywords: • serum lipid • metabolic syndrome • hypertension • neoplasm • esophagus • stomach

Word count for body text: 3164

Running head: Metabolic Syndrome and Esophageal and Gastric Adenocarcinoma

Abstract

Background: The role of the metabolic syndrome in the etiology of esophageal and gastric cancer is unclear.

Methods: This was a large nationwide cohort study based on data from 11 prospective population-based cohorts in Norway with long-term follow-up, the Cohort of Norway (CONOR) and the third Nord-Trøndelag Health Study (HUNT3). The metabolic syndrome was assessed by objective anthropometric and metabolic biochemical measures and was defined by the presence of at least three of the following five factors: increased waist circumference, elevated triglycerides, low high-density lipoprotein cholesterol, hypertension, and high glucose. Newly diagnosed cases of esophageal adenocarcinoma, esophageal squamous-cell carcinoma and gastric adenocarcinoma were identified from the Norwegian Cancer Registry. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models with adjustment for potential confounders.

Result: Among 192,903 participants followed up for an average of 10.6 years, 62 developed esophageal adenocarcinoma, 64 had esophageal squamous-cell carcinoma and 373 had gastric adenocarcinoma. The metabolic syndrome was significantly associated with an increased risk of gastric adenocarcinoma (HR=1.44, 95% CI: 1.14-1.82), but not associated with esophageal adenocarcinoma (HR=1.32, 95% CI: 0.77-2.26) or esophageal squamous-cell carcinoma (HR=1.08, 95% CI: 0.64-1.83). Increased waist circumference was associated with an increased HR of esophageal adenocarcinoma (HR=2.48, 95% CI: 1.27-4.85). No significant association was found between any single component of the metabolic syndrome and risk of esophageal squamous-cell carcinoma. High waist circumference (HR=1.71, 95% CI: 1.05-2.80), hypertension (HR=2.41, 95% CI: 1.44-4.03) and non-fasting glucose (HR=1.74, 95% CI: 1.18-2.56) were also related to an increased risk of gastric adenocarcinoma in women, but not in men.

Conclusion: Metabolic syndrome was associated with an increased risk of gastric adenocarcinoma in women. Of the individual components of the metabolic syndrome, high waist circumference was positively associated with risk of esophageal adenocarcinoma. Positive associations were also observed for women between high waist circumference, hypertension, high non-fasting glucose and risk of gastric adenocarcinoma. However, further evidence is warranted due to the limited number of cases and the inability to effectively identify gastric cardia adenocarcinoma.

Introduction

Esophageal and gastric cancers are two of the most common cancers worldwide. Globally, esophageal cancer ranks eighth in incidence and sixth in cancer-related mortality, while gastric cancer ranks fourth and second, respectively.(1) The precise etiology for these tumors still remains unclear. Metabolic syndrome, which is defined by the presence of at least 3 out of the 5 factors abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol (HDL), hypertension, and high fasting glucose,(2) is becoming an almost ubiquitous severe health issue across the globe. It is estimated that more than 40% of U.S. residents over the age of 60 years have metabolic syndrome,(3) with a prevalence of approximately 25% in European and Latin populations.(4, 5) Originally, the concern regarding metabolic syndrome was primarily focused on its contribution to increased cardiovascular disease and type 2 diabetes mellitus risk. However, recent evidence has shown a carcinogenic role of the metabolic syndrome in certain types of cancer.(6-11) However to date, epidemiological studies on metabolic syndrome and gastroesophageal cancer are sparse. There is, to the best of our knowledge, only one study that has addressed the association between the metabolic syndrome and risk of esophageal cancer, and one of gastric cancer.(12, 13) Abdominal obesity has been suggested to contribute to the increased risk of esophageal and gastric adenocarcinoma,(14, 15) while the role of other variables that constitute the metabolic syndrome is uncertain. The aim of the present study was to investigate the relation between the metabolic syndrome and the risk of esophageal adenocarcinoma, esophageal squamous-cell carcinoma and gastric adenocarcinoma using a large population-based cohort study with long-term follow-up in Norway.

Methods

Study design and participants

This study was based on the Cohort of Norway (CONOR) and the third Nord-Trøndelag Health Study (HUNT3). The details of both these cohorts have been described previously.^(16, 17) In brief, CONOR is a collaborative project between the Norwegian Institute of Public Health and universities in Oslo, Bergen, Trondheim, and Tromsø, where data from 10 regional health surveys have been combined into one national database. The study started in 1994 and includes individuals from 20 to 103 years of age. Among 309,742 invited individuals of ages ≥ 20 years, 180,546 (58.3%) participated in CONOR.¹⁶ The HUNT study is an ongoing large total population-based cohort started in the 1980s in Nord-Trøndelag County, Norway. Two waves of HUNT surveys are included in the current study: HUNT2 (1995-1997) and HUNT3 (2006-2008). Every resident of Nord-Trøndelag County aged 20 years or older (or turning 20 years during the year of survey) was invited. The participants in HUNT2 (65,237) are included in CONOR, but in the present study the participants in HUNT3 are also included. In HUNT3, all 93,860 eligible residents above 20 years in the county were invited and 50,807 of them participated (54.1%).⁽¹⁷⁾

In both the CONOR and HUNT3 surveys, the comprehensive data collection came from questionnaires, clinical examinations and blood samples, which included waist and hip circumference, serum level of HDL, triglycerides, height, weight, blood pressure, and serum level of non-fasting glucose. The present study was approved by the Regional Committee for Medical and Health Research Ethics, Central (ID 2012/853).

Study sample

37,059 of the 50,807 HUNT3 participants also participated in HUNT2, which is included in CONOR. Therefore, the 13,748 participants who participated only in HUNT3 were added to the total CONOR sample to comprise the current study. The final study cohort included 194,294 participants from CONOR (n=180,546) and HUNT3 (n=13,748) together. After exclusion of participants without a participation date (n=53), or any cancer before the study recruitment (n=1,261), 192,903 participants remained for the final analysis.

Case ascertainment and follow-up

All newly diagnosed cases of esophageal adenocarcinoma, esophageal squamous-cell carcinoma and gastric adenocarcinoma were retrieved from linkage to the Cancer Registry of Norway, which was established in 1951 and is considered a complete and reliable registry.(18)

Esophageal cancer was identified by the seventh revision of International Classification of Diseases (ICD-7) code '150' and further categorized into adenocarcinoma and squamous-cell carcinoma by morphological codes in International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (Supplementary Table 1).(19) Gastric cancer was defined with ICD-7 code '151'. Due to the fact that gastric cardia cancer was included in the same code (ICD-7 code '1512') as cancer in the fundus and upper stomach, it was not possible to separate gastric cardia and non-cardia cancer. Gastric adenocarcinoma histology was identified among all gastric cancers followed by the relevant morphological code in ICD-O-3. Determination of date of death and emigration was accomplished from Statistics Norway. All participants were followed up from the date of entry into the cohort until the date of diagnosis of esophageal adenocarcinoma, esophageal squamous-cell carcinoma, or gastric adenocarcinoma, any other cancer, death, emigration, or the end of the study period (31st, December, 2010), whichever came first. To

avoid detection bias, we also conducted a sensitivity analysis excluding all persons-years during the first two years of follow-up. Since the results of the main analysis and the sensitivity analysis were similar, we present the results of the sensitivity results in supplementary Table 2.

Measurement of individual components of metabolic syndrome

Blood samples were collected and the serum was separated by centrifuging at the screening site. The Department of Clinical Chemistry, Ullevål or University Hospital, Oslo, performed all laboratory assessments for CONOR, except for HUNT2.(17) Study samples from HUNT2 and HUNT3 were analyzed at the Department of Clinical Chemistry, Levanger Hospital. Comparisons between the blood-samples analyzed in the different laboratories revealed small differences.(17)

Systolic and diastolic blood pressure was measured using an automatic device (Dinamap, Criticon, USA). Height and weight were measured with the participants wearing light clothes without shoes. Waist and hip circumference were measured with a band to the nearest full centimeter, with the participants standing and with the arms hanging relaxed. The waist circumference was measured at the height of the umbilicus, and the hip circumference was measured at the thickest part of the hip.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using Cox proportional hazard models, with follow-up of person-days as the underlying time metric.(20) The proportional hazards assumption was tested for potential confounders (presented below), and all variables conformed to the assumption of proportionality. The exposure to metabolic syndrome

related factors was categorized into groups based on clinical cut-off points defined in 2009 for the metabolic syndrome(2): waist circumference (women <80 cm, men <94 cm, or women \geq 80 cm, men \geq 94 cm), HDL (women \geq 1.3 mmol/L, men \geq 1.0 mmol/L, or women <1.3 mmol/L, men <1.0 mmol/L), triglycerides (<1.7 mmol/L or \geq 1.7 mmol/L), and fasting glucose (<5.6 mmol/L or \geq 5.6 mmol/L). Hypertension was defined as systolic blood pressure \geq 130 mm Hg, or diastolic blood pressure \geq 85 mm Hg. The metabolic syndrome was defined based on previous research by the presence of three or more of the following five factors: increased waist circumference, elevated triglycerides, low HDL, hypertension, and high fasting glucose.(2) In the current study, we used non-fasting glucose as an index for fasting glucose, adjusting for time (in hours) since last meal. As previous studies have indicated a women-specific effect of metabolic syndrome on the risk of gastric adenocarcinoma, we also categorized the analysis by gender.

Possible confounding or effect modification by the following known risk factors for esophageal or gastric cancer were considered: age (categorized into two groups: <60 or \geq 60 years), sex (female or male), education (primary/secondary school, high school, or university), body mass index (BMI) (<25, 25-29.9, or \geq 30 kg/m²), tobacco smoking status (yes or no), alcohol drinking (>4, 4, 2-3, 1 times per week, or none), and family history of cancer (yes or no). The basic model included adjustment for age and sex only, while the full model adjusted for all variables listed above. In the analysis of non-fasting glucose, time since last meal (<3, 3-5, or \geq 5 hours) was added into the full model. Since exposure to non-fasting glucose, waist circumference, education and alcohol consumption had more than 10% missing values, we developed various strategies to reduce the potential bias that could be induced by missing values. For the continuous variables, non-fasting glucose and waist circumference, multiple imputation was used to impute the missing

values.(21) With this approach, a model is posited for the association between missing values and recorded values, using records in which the non-fasting glucose and waist circumference data are available. All potential confounders mentioned above, as well as cancer diagnosis status and metabolic syndrome components were accounted for in this model. The model is used to generate several replicate ‘completed’ data sets (n=5), where the imputed values were produced to replace those missing values. By combining results from these completed data sets, valid statistical inferences of parameters of interest are then generated using multiple imputation rules.(21) For the categorical variables education and alcohol consumption, we kept all the missing values as a separate category. The SAS Statistical Package (version 9.2, SAS institute, Gary, NC) was used for all analyses.

Results

Study participants

During follow-up of 192,903 participants for an average of 10.6 years (2,050,335 person-years at risk), 62 esophageal adenocarcinoma, 64 esophageal squamous-cell carcinoma, and 373 gastric adenocarcinoma were identified. Baseline characteristics of the cohort members are shown in Table 1. The mean age at entrance into the cohort was 49.5 years, while the mean age for cancer cases was 65.0 years. Cases of esophageal adenocarcinoma and gastric adenocarcinoma had higher frequencies of metabolic syndrome and higher waist circumference than the non-cases group (all p value<0.05, data not shown). Hypertension was overrepresented in all cancer case groups, compared to the control cohort (p<0.05, data not shown). Distribution of high level of non-fasting glucose was highest among cases of esophageal squamous-cell carcinoma and gastric adenocarcinoma compared to the control cohort (all p values<0.05, data not shown).

Metabolic syndrome and risk of esophageal adenocarcinoma

The metabolic syndrome as a composite index was not statistically significantly associated with an increased risk of esophageal adenocarcinoma (HR 1.32, 95% CI: 0.77-2.26) (Table 2).

Compared to a lower waist circumference, a higher waist circumference was followed by an increased HR of this cancer (HR 2.48, 95% CI: 1.27- 4.85). None of the other four components of the metabolic syndrome (HDL, triglycerides, hypertension, and glucose) were significantly associated with any increased risk of esophageal adenocarcinoma (Table 2).

Metabolic syndrome and risk of esophageal squamous-cell carcinoma

The metabolic syndrome was not associated with increased risk of esophageal squamous-cell carcinoma (HR 1.08, 95% CI: 0.64-1.83). High glucose levels were borderline associated with an increased risk of this cancer (HR 1.70, 95% CI: 1.00-2.90). There were no clear associations with any of the other constituents of the metabolic syndrome (Table 2).

Metabolic syndrome and risk of gastric adenocarcinoma

In the total population, presence of the metabolic syndrome was associated with a 44% increased risk of gastric adenocarcinoma (HR 1.44, 95% CI 1.14-1.82). When the analysis was stratified by sex, 64% (HR 1.64, 95% CI 1.07-2.49), and 36% (HR 1.36, 95% CI 1.01-1.84) increased risks were observed in women and men, respectively. Among women, increased HRs of this cancer were also found for participants with higher waist circumference (HR 1.71, 95% CI 1.05-2.80), hypertension (HR 2.41, 95% CI 1.44-4.03) and higher glucose levels (HR 1.74, 95% CI 1.18-2.56) (Table 3). No single component of the metabolic syndrome was associated with risk of gastric adenocarcinoma in men.

Discussion

An increased risk of gastric adenocarcinoma was identified with the presence of the metabolic syndrome, while no such statistically significant associations were found between the metabolic syndrome and risk of esophageal adenocarcinoma or squamous-cell carcinoma. Among the individual components of the metabolic syndrome, high waist circumference was associated with an increased risk of esophageal adenocarcinoma, and high waist circumference, hypertension, and high glucose with an increased risk of gastric adenocarcinoma in women, but not men.

Strengths of the present study include the prospective and population-based design, the detailed and objectively assessed exposure information of components of the metabolic syndrome, the reliable identification of cancer cases through the national cancer registry, the virtually complete follow-up of all cohort members, and the availability of several confounders. However, some potential confounders, i.e. gastroesophageal reflux and *Helicobacter pylori* infection are not available. Moreover, the variables education and alcohol drinking had more than 10% of missing values, leaving a risk for residual confounding. Although this study included over 2 million person-years at risk, the limited number of cancer cases is a weakness, reducing the power to find weaker associations. Another limitation of the exposure assessment was that glucose levels were not fully fasting values. However, we added the time (in hours) since last meal in the adjustment in order to attenuate the potential bias. Since the misclassification of the exposure in a prospective study design would be similarly distributed among cases and controls, the influence on the results would tend to be non-differential. Finally, since the cardia cancer is different from the non-cardia cancer in clinical and pathological features, as well as in prognosis, we cannot rule

out potential selection bias due to the fact that cardia cancer could not be distinguished from overall gastric cancer.

Although we did not observe any statistically significant association between the metabolic syndrome and esophageal adenocarcinoma, the component high waist circumferences was a risk factor. The latter observation gains support from other studies.(14, 22, 23) After 11.3 years follow-up in 41,295 individuals, an Australian study reported an HR of 2.9 (95% CI 1.2-6.9) when comparing the highest and the lowest tertile of waist circumference.(22) In the European Prospective Investigation into Cancer and Nutrition study, 346,544 adults were followed for 8.9 years and revealed a relative risk of 3.07 (95% CI 1.35-6.98) of esophageal or gastroesophageal junctional adenocarcinoma comparing participants in the highest and lowest quintile of waist circumference.(23) There are several potential mechanisms behind this association, including an increased intra-abdominal pressure caused by abdominal obesity, which increases the risk of gastroesophageal reflux, a strong risk factor for esophageal adenocarcinoma.(24-26) Abdominal obesity is also associated with increased hormone levels, such as insulin-like growth factor and adiponectin, which are known to influence cell division, cell death, and healing.(27, 28)

It should be noticed that, the CONOR has been included in a pooling study by Lindkvist *et al.* to investigate the association between metabolic syndrome and risk of esophageal cancer.(12)

However, two key components of the metabolic syndrome, waist circumference and HDL, were not applied in that study. This may have led to misclassification of the metabolic syndrome and limited the scientific value of the study. In line with the previous study by Lindkvist *et al.*,(12) we did not observe a significant association between overall metabolic syndrome and risk of esophageal squamous-cell carcinoma. Waist circumference, HDL, triglycerides, hypertension and

non-fasting glucose were also not associated with esophageal squamous-cell carcinoma in the current study. In contrast, Lindkvist and his colleagues found a strong and dose dependent association between mid-blood pressure ($(\text{systolic BP} + \text{diastolic BP})/2$) and risk of esophageal squamous-cell carcinoma, but alcohol consumption was considered a potential confounding factor that they were not able to adjust for.(12) An increased risk of esophageal cancer in general related to hypertension diagnosed below the age of 60 years was recently reported,(29) but to date, no other studies have been able to explore the association between hypertension and esophageal squamous-cell carcinoma.

The finding of an association between the metabolic syndrome and the risk of gastric adenocarcinoma is interesting.(13) In the only previous study addressing this association, z-score standardization was used to create a composite metabolic syndrome score, which was found to be borderline associated with risk of gastric adenocarcinoma in women, but not men. In contrast, we found that metabolic syndrome as an overall condition was associated with gastric adenocarcinoma in both women and men. The chronic inflammation induced by the metabolic syndrome and its mediators might be involved in tumor development.(30)

Participants with high waist circumference were found to have a 50% higher risk of gastric adenocarcinoma. There is strong evidence showing the positive association between esophageal and gastric cardia adenocarcinoma and abdominal obesity, but it remains unclear whether there is an association with gastric non-cardia adenocarcinoma. In a large prospective study in the U.S. including 191 cardia and 125 non-cardia cancers, a positive association between cardia gastric cancer and waist circumference (HR 2.22, 95% CI 1.4-3.5) was observed. No association was observed for abdominal obesity and non-cardia gastric cancer.(31) However, in the current study

we could not conclude whether the observed association was relevant only for cardia cancer or both cardia and non-cardia cancer. Interestingly, this association seems to be women-specific, and not seen in men. Possible mechanisms linking obesity and gastric cancer may include obesity associated gastro-esophageal reflux, abnormal gastric motility, insulin resistance, altered levels of metabolic endogenous hormones, and an abnormally increased blood level of insulin-like growth factor (IGF).(32) Recent evidence has revealed an increased prevalence of *Helicobacter pylori* infection in the obese patients, providing another indication for the increased incidence of gastric cancer in obese population. Further research with separate cardia and non-cardia cancer cases is needed to clarify the potential association with increased waist circumference.

Our finding of a moderate association between hypertension and risk of gastric adenocarcinoma is partly supported by the previous study, which suggests that patients with self-reported hypertension history may be at a 2-fold increased risk of adenocarcinoma of esophagus and gastric cardia.(33) Hypertension is the most prevalent cardiovascular condition in the United States and affects over 60 million people. Men have a higher prevalence of hypertension than women (38% versus 29%). The prevalence of elevated blood pressure in American youth was 9.3% among female subjects and 18.5% among male subjects.(34) The mechanism is unclear, but it is plausible that hypertension and malignancy might share some common biochemical pathways. For example, increased production of inositol triphosphate and increased levels of cytosolic calcium are likely to be involved in the pathogenesis of hypertension and in the early events of cell proliferation that are activated by endogenous mitogens and oncogenes.(35)

Among other individual components of the metabolic syndrome in the previous study,(13) fasting glucose was the single factor that was significantly associated with the risk of gastric

adenocarcinoma in women. This finding is supported by our results, with increased risk estimates for high glucose levels (non-fasting) and risk of gastric adenocarcinoma. Glucose has also been indicated as an independent risk factor for gastric cancer in other studies.(36) The role that high serum glucose level plays in the development of gastric adenocarcinoma needs to be assessed further in a larger epidemiological study.

In conclusion, this population-based cohort study with objective assessment of all components of the metabolic syndrome revealed an association with gastric adenocarcinoma in women, but not so clearly for esophageal adenocarcinoma or squamous cell carcinoma. Of the individual components of the metabolic syndrome, high waist circumference was associated with an increased risk of esophageal adenocarcinoma, while women with high waist circumference, hypertension, and high glucose were under higher risk of gastric adenocarcinoma. There is, however, a need for further large-scale and prospective studies to demonstrate any role of the metabolic syndrome in the etiology of esophageal and gastric cancer.

Financial Support: This work was supported by the Faculty Funds for Partial Financing of New Doctoral Students from Karolinska Institutet (12059012 /KID-medel 2010); the Swedish Research Council (SIMSAM); and the Swedish Society of Medicine.

Conflict of Interest: The authors declare that they have no conflict of interests.

Acknowledgement: The authors wish to acknowledge the services of CONOR, the contributing research centers delivering data to CONOR and all the study participants. The following cohorts from CONOR were used in the analysis: Tromsø IV and V, TROFINN, HUNT2, Oslo I, HUBRO, The Immigrant Study, MoRo, Oslo II, OPPHED, and HUSK

The Nord-Trøndelag Health Study (The HUNT Study) is performed through collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

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Table 1. Baseline characteristics.

	Esophageal adenocarcinoma	Esophageal squamous-cell carcinoma	Gastric adenocarcinoma	Total cohort
Subject, n	62	64	373	192,903
Average follow up years (\pmstd[†])	6.9 (\pm 3.8)	5.1 (\pm 3.6)	5.9 (\pm 3.9)	10.6 (\pm 4.0)
Person years	428	325	1,612	2,050,335
Age at participation (\pmstd[†])	64.1 (\pm 10.2)	65.0 (\pm 11.4)	65.1 (\pm 11.8)	49.5 (\pm 15.7)
Sex, n (%)				
1 Women	7 (11.3%)	27 (42.2%)	153 (41.0%)	99,845 (51.8%)
2 Men	55 (88.7%)	37 (57.8%)	220 (59.0%)	93,058 (48.2%)
BMI				
1 (<25 kg/m ²)	8 (12.9%)	32 (50.0%)	136 (36.5%)	83,542 (43.3%)
2 (25-30 kg/m ²)	46 (74.2%)	22 (34.4%)	165 (44.2%)	78,488 (40.7%)
3 (\geq 30 kg/m ²)	8 (12.9%)	10 (15.6%)	72 (19.3%)	29,667 (15.4%)
<i>Missing</i>	0	0	0	1,206 (0.6%)
Smoking status, n (%)				
1 No	43 (69.4%)	25 (39.1%)	250 (67.0%)	129,363 (67.1%)
2 Yes	19 (30.6%)	38 (59.4%)	120 (32.2%)	55,186 (28.6%)
<i>Missing</i>	0	1 (1.5%)	3 (0.8%)	8,354 (4.3%)
Education				
1 (primary/secondary school)	13 (21.0%)	24 (37.5%)	157 (42.1%)	43,639 (22.6%)
2 (high school)	20 (32.2%)	11 (17.2%)	69 (18.5%)	57,210 (30.6%)
3 (university)	4 (6.5%)	5 (7.8%)	23 (6.2%)	21,137 (11.0%)
<i>Missing</i>	25 (40.3%)	24 (37.5%)	124 (33.2%)	70,917 (36.8%)
Family cancer history				
1 No	47 (75.8%)	46 (71.9%)	253 (67.8%)	144,534 (74.9%)
2 Yes	15 (24.2%)	18 (28.1%)	120 (32.2%)	48,369 (25.1%)
Alcohol drinking (times/week)				
1 (>4 times)	18 (29.0%)	14 (21.9%)	36 (9.7%)	28,669 (14.9%)
2 (4 times)	10 (16.1%)	8 (12.5%)	63 (16.9%)	34,184 (17.7%)
3 (2-3 times)	11 (17.7%)	11 (17.2%)	60 (16.1%)	41,086 (21.3%)
4 (1 time)	5 (8.1%)	2 (3.1%)	23 (6.0%)	17,599 (9.1%)
5 (none)	12 (19.4%)	17 (26.5%)	128 (34.3%)	52,299 (27.1%)
<i>Missing</i>	6 (9.7%)	12 (18.8%)	54 (16.0%)	19,066 (9.9%)
Metabolic syndrom[‡]				
1 No	25 (40.3%)	33 (51.5%)	161 (43.2%)	117,376 (60.9%)
2 Yes	37 (59.7%)	31 (48.5%)	212 (56.8%)	75,686 (39.1%)
Waist circumference				
1 (women<80, men< 94 cm)	12 (19.4%)	24 (37.5%)	114 (30.6%)	85,266 (44.2%)
2 (women \geq 80, men \geq 94 cm)	50 (80.6%)	40 (62.5%)	259 (69.4%)	107,637 (55.8%)
High-density lipoprotein cholesterol (HDL)				
1 (women \geq 1.3, men \geq 1.0 mmol/L)	52 (83.9%)	52 (81.3%)	279 (74.8%)	145,286 (75.3%)
2 (women<1.3, men<1.0 mmol/L)	10 (16.1%)	11 (17.2%)	90 (24.1%)	46,671 (24.2%)
Triglycerides				
1 (<1.7 mmol/L)	29 (46.8%)	43 (67.2%)	211 (56.7%)	121,012 (62.7%)
2 (\geq 1.7 mmol/L)	33 (53.2%)	21 (32.8%)	160 (42.9%)	71,216 (36.9%)
	0	0	2 (0.4%)	675 (0.4%)
Hypertension[§]				
1 No	17 (27.4%)	13 (20.3%)	78 (20.9%)	86,243 (44.7%)
2 Yes	45 (72.6%)	51 (79.7%)	295 (79.1%)	106,660 (55.3%)
Non-fasting glucose				
1 (<5.6 mmol/L)	31 (50.0%)	27 (42.2%)	173 (46.4%)	117,381 (60.9%)
2 (\geq 5.6 mmol/L)	31 (50.0%)	37 (57.8%)	200 (53.6%)	75,522 (39.1%)

[†] Standard deviation

[‡] Metabolic syndrome was defined by the presence of \geq 3 of following 5 factors: increased waist circumference (men \geq 94 cm, women \geq 80 cm), elevated triglycerides (\geq 1.7 mmol/L), low HDL (men<1.0 mmol/L, women<1.3 mmol/L), hypertension (systolic blood pressure \geq 130 mm Hg, or diastolic blood pressure \geq 85 mm Hg), and high non-fasting glucose (\geq 5.6 mmol/L).

§ Hypertension was defined with systolic blood pressure ≥ 130 mm Hg, or diastolic blood pressure ≥ 85 mm Hg.

Table 2. Hazard ratio (HR) with 95% confidence interval for incident esophageal adenocarcinoma and esophageal squamous-cell carcinoma related to metabolic syndrome.

Exposure	Esophageal adenocarcinoma			Esophageal squamous-cell carcinoma		
	No.	HR [†]	HR [‡]	No.	HR [†]	HR [§]
Metabolic syndrome[#]						
No	25	1.0	1.0	33	1.0	1.0
Yes	37	1.54 (0.93-2.57)	1.32 (0.77-2.26)	31	0.98 (0.60-1.61)	1.08 (0.64-1.83)
Waist circumference						
Women <80 cm, men <94 cm	12	1.0	1.0	24	1.0	1.0
Women ≥ 80 cm, men ≥ 94 cm	50	3.05 (1.62-5.75)	2.48 (1.27-4.85)	40	1.05 (0.63-1.75)	1.19 (0.71-2.00)
HDL						
Women ≥ 1.3 mmol/L, men ≥ 1.0 mmol/L	52	1.0	1.0	52	1.0	1.0
Women <1.3 mmol/L, men <1.0 mmol/L	10	0.87 (0.44-1.72)	0.76 (0.38-1.52)	11	0.77 (0.40-1.49)	0.70 (0.35-1.40)
Triglycerides						
<1.7 mmol/L	29	1.0	1.0	43	1.0	1.0
≥ 1.7 mmol/L	33	1.35 (0.82-2.22)	1.15 (0.69-1.91)	21	0.65 (0.38-1.10)	0.68 (0.40-1.15)
Hypertension[¶]						
No	17	1.0	1.0	13	1.0	1.0
Yes	45	0.90 (0.51-1.60)	0.82 (0.46-1.46)	51	1.52 (0.80-2.88)	1.62 (0.85-3.08)
Non-fasting glucose[^]						
<5.6 mmol/L	31	1.0	1.0	27	1.0	1.0
≥ 5.6 mmol/L	31	1.09 (0.66-1.80)	1.06 (0.63-1.78)	37	1.63 (0.99-2.69)	1.70 (1.00-2.90)

† Adjusted for age (<60, ≥ 60 years), sex (women, men).

‡ Adjusted for age (<60, ≥ 60 years), sex (women, men), BMI (<25, 25-30, ≥ 30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes); family cancer history (no, yes).

§ Adjusted for age (<60, ≥ 60 years), sex (women, men), BMI (<25, 25-30, ≥ 30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes), alcohol intake (>4, 4, 2-3, 1 times per week, and none), family cancer history (no, yes).

Metabolic syndrome was defined by the presence of ≥ 3 of following 5 factors: increased waist circumference (men ≥ 94 cm, women ≥ 80 cm), elevated triglycerides (≥ 1.7 mmol/L), low HDL (men <1.0 mmol/L, women <1.3 mmol/L), hypertension (systolic blood pressure ≥ 130 mm Hg, or diastolic blood pressure ≥ 85 mm Hg), and high non-fasting glucose (≥ 5.6 mmol/L).

^ Additionally adjusted for time since last meal (<3, 3-5, ≥ 5 hours).

Table 3. Hazard ratio (HR) with 95% confidence interval for incident gastric adenocarcinoma related to metabolic syndrome.

Exposure	Total			Women			Men		
	No.	HR [†]	HR [‡]	No.	HR [†]	HR [§]	No.	HR [†]	HR [§]
Metabolic syndrome#									
No	161	1.0	1.0	66	1.0	1.0	95	1.0	1.0
Yes	212	1.38 (1.12-1.70)	1.44 (1.14-1.82)	87	1.40 (1.00-1.95)	1.64 (1.07-2.49)	125	1.36 (1.04-1.78)	1.36 (1.01-1.84)
Waist circumference									
Men<94 cm, women<80 cm	114	1.0	1.0	40	1.0	1.0	74	1.0	1.0
Men≥94 cm, women≥80 cm	259	1.43 (1.14-1.79)	1.47 (1.14-1.90)	113	1.33 (0.92-1.92)	1.71 (1.05-2.80)	146	1.49 (1.12-1.97)	1.38 (1.00-1.91)
HDL									
Men≥1.0 mmol/L, women≥1.3 mmol/L	279	1.0	1.0	111	1.0	1.0	168	1.0	1.0
Men<1.0 mmol/L, women<1.3 mmol/L	90	1.20 (0.94-1.54)	1.18 (0.92-1.50)	42	1.00 (0.70-1.42)	1.02 (0.67-1.56)	48	1.41 (1.02-1.95)	1.34 (0.97-1.87)
Triglycerides									
<1.7 mmol/L	211	1.0	1.0	95	1.0	1.0	116	1.0	1.0
≥1.7 mmol/L	160	1.02 (0.83-1.26)	0.99 (0.80-1.23)	58	1.04 (0.74-1.46)	1.00 (0.67-1.49)	102	1.00 (0.77-1.31)	0.95 (0.72-1.25)
Hypertension[□]									
No	78	1.0	1.0	32	1.0	1.0	46	1.0	1.0
Yes	295	1.54 (1.19-2.01)	1.52 (1.16-1.98)	121	2.09 (1.35-3.22)	2.41 (1.44-4.03)	174	1.27 (0.91-1.77)	1.24 (0.88-1.73)
Non-fasting glucose[^]									
<5.6 mmol/L	173	1.0	1.0	69	1.0	1.0	104	1.0	1.0
≥5.6 mmol/L	200	1.33 (1.08-1.63)	1.36 (1.10-1.69)	84	1.56 (1.13-2.15)	1.74 (1.18-2.56)	116	1.19 (0.91-1.55)	1.22 (0.92-1.62)

[†] Adjusted for age (<60, ≥60 years).

[‡] Adjusted for age (<60, ≥60 years), sex (women, men), BMI (<25, 25-30, ≥30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes); family cancer history (no, yes).

[§] Adjusted for age (<60, ≥60 years), BMI (<25, 25-30, ≥30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes); family cancer history (no, yes).

Metabolic syndrome was defined by the presence of ≥ 3 of following 5 factors: increased waist circumference (men ≥ 94 cm, women ≥ 80 cm), elevated triglycerides (≥ 1.7 mmol/L), low HDL (men < 1.0 mmol/L, women < 1.3 mmol/L), hypertension (systolic blood pressure ≥ 130 mm Hg, or diastolic blood pressure ≥ 85 mm Hg), and high non-fasting glucose (≥ 5.6 mmol/L).

^ Additionally adjusted for time since last meal (< 3 , 3-5, ≥ 5 hours).

Supplemental table 1. List of morphological codes in ICD-O-3 used to differentiate the histological types of esophageal and gastric cancer

Adenocarcinoma	
8140/3	Adenocarcinoma, NOS
8141/3	Scirrhus adenocarcinoma
8144/3	Adenocarcinoma, intestinal type (C16._)
8145/3	cardinoma, diffuse type (adenocarcinoma, diffuse type) (C16._)
8147/3	basal cell adenocarcinoma
8150/3	Islet cell carcinoma (C25._)
8154/3	Mixed islet cell and exocrine adenocarcinoma (C25._)
8190/3	Trabecular adenocarcinoma
8210/3	adenocarcinoma in adenomatous polyp
8211/3	tubular adenocarcinoma
8214/3	parietal cell carcinoma (parietal cell adenocarcinoma) (C16._)
8215/3	Adenocarcinoma of anal glands (C21.1)
8220/3	Adenomatous polyposis coli (C18._)
8221/3	adenocarcinoma in multiple adenomatous polys
8250/3	Bronchiolo-alveolar adenocarcinoma, NOS (C34._)
8251/3	Alveolar adenocarcinoma (C34._)
8255/3	adenocarcinoma with mixed subtypes
8260/3	Papillary adenocarcinoma, NOS
8261/3	adenocarcinoma in villous adenoma
8262/3	villous adenocarcinoma
8263/3	adenocarcinoma in tubulovillous adenoma
8270/3	Chromophobe carcinoma (C75.1) (Chromophobe adenocarcinoma (C75.1))
8290/3	Oxyphilic adenocarcinoma
8300/3	Basophil carcinoma (C75.1) (Basophil adenocarcinoma (C75.1); Mucoïd cell adenocarcinoma (C75.1))
8310/3	clear cell adenocarcinoma
8320/3	Granular cell carcinoma (Granular cell adenocarcinoma)
8322/3	Water-clear cell adenocarcinoma (C75.0)
8323/3	mix cell adenocarcinoma
8330/3	Follicular adenocarcinoma, NOS (C73.9)
8331/3	Follicular adenocarcinoma, well differentiated (C73.9)
8332/3	Follicular adenocarcinoma, trabecular (C73.9)
8333/3	Fetal adenocarcinoma
8380/3	Endometrioid adenocarcinoma, NOS
8382/3	Endometrioid adenocarcinoma, secretory variant
8383/3	Endometrioid adenocarcinoma, ciliated cell variant
8384/3	Adenocarcinoma, endocervical type
8400/3	Sweat gland adenocarcinoma (C44._)
8401/3	Apocrine adenocarcinoma
8408/3	Eccrine papillary adenocarcinoma (C44._) SKIN
8410/3	Sebaceous adenocarcinoma (C44._) SKIN
8413/3	Eccrine adenocarcinoma (C44._)
8420/3	Ceruminous adenocarcinoma (C44.2)
8480/3	mucinous adenocarcinoma
8481/3	mucin-producing adenocarcinoma
8482/3	Mucinous adenocarcinoma, endocervical type
8490/3	signet ring cell carcinoma
8503/2	Noninfiltrating intraductal papillary adenocarcinoma (C50._)
8503/3	Intraductal papillary adenocarcinoma (C50._)

8504/3	Intracystic carcinoma, NOS (Intracystic papillary adenocarcinoma)
8510/3	Medullary carcinoma, NOS (Medullary adenocarcinoma)
8525/3	Polymorphous low grade adenocarcinoma
8530/3	Inflammatory carcinoma (C50. _) (Inflammatory adenocarcinoma (C50. _))
8571/3	adenocarcinoma with cartilaginous and osseous metaplasia
8572/3	adenocarcinoma with spindle cell metaplasia
8573/3	adenocarcinoma with apocrine metaplasia
8574/3	Adenocarcinoma with neuroendocrine differentiation
8576/3	Hepatoid adenocarcinoma

Esophageal squamous-cell carcinoma

8052/3	Papillary squamous cell carcinoma
8070/3	squamous-cell carcinoma, NOS
8071/3	squamous-cell carcinoma, keratinizing
8072/3	squamous cell carcinoma, large cell, nonkeratinizing, NOS
8073/3	Squamous cell carcinoma, small cell, nonkeratinizing
8074/3	squamous cell carcinoma, spindle cell
8075/3	Squamous cell carcinoma, microinvasive
8076/3	Squamous cell carcinoma, microinvasive
8078/3	squamous cell carcinoma with horn formation

Supplemental table 2. Hazard ratio (HR) with 95% confidence interval for incident esophageal adenocarcinoma and esophageal squamous-cell carcinoma related to metabolic syndrome with first two years follow-up excluded.

Exposure	Esophageal adenocarcinoma			Esophageal squamous-cell carcinoma		
	No.	HR [†]	HR [‡]	No.	HR [†]	HR [§]
Metabolic syndrome#						
No	21	1.0	1.0	24	1.0	1.0
Yes	31	1.53 (0.88-2.68)	1.07 (0.52-2.21)	19	0.83 (0.45-1.53)	2.52 (0.94-6.74)
Waist circumference						
Women<80 cm, men<94 cm	10	1.0	1.0	15	1.0	1.0
Women≥80 cm, men≥94 cm	42	3.08 (1.54-6.17)	1.79 (0.76-4.18)	28	1.23 (0.65-2.32)	2.03 (0.79-5.20)
HDL						
Women≥1.3 mmol/L, men≥1.0 mmol/L	45	1.0	1.0	36	1.0	1.0
Women<1.3 mmol/L, men<1.0 mmol/L	7	0.70 (0.32-1.57)	0.46 (0.16-1.33)	6	0.63 (0.26-1.51)	0.65 (0.19-2.24)
Triglycerides						
<1.7 mmol/L	24	1.0	1.0	27	1.0	1.0
≥1.7 mmol/L	28	1.38 (0.80-2.38)	0.86 (0.43-1.71)	16	0.78 (0.42-1.45)	1.31 (0.57-3.00)
Hypertension[□]						
No	15	1.0	1.0	11	1.0	1.0
Yes	37	0.84 (0.45-1.57)	0.66 (0.31-1.44)	32	1.11 (0.54-2.29)	3.39 (0.96-11.95)
Non-fasting glucose[^]						
<5.6 mmol/L	27	1.0	1.0	17	1.0	1.0
≥5.6 mmol/L	25	1.00 (0.58-1.73)	0.86 (0.43-1.72)	26	1.82 (0.98-3.36)	3.00 (1.07-8.46)

† Adjusted for age (<60, ≥60 years), sex (women, men).

‡ Adjusted for age (<60, ≥60 years), sex (women, men), BMI (<25, 25-30, ≥ 30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes); family cancer history (no, yes).

§ Adjusted for age (<60, ≥60 years), sex (women, men), BMI (<25, 25-30, ≥ 30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes), alcohol intake (>4, 4, 2-3, 1 times per week, and none), family cancer history (no, yes).

Metabolic syndrome was defined by the presence of ≥3 of following 5 factors: increased waist circumference (men≥94 cm, women≥80 cm), elevated triglycerides (≥1.7 mmol/L), low HDL (men<1.0 mmol/L, women<1.3 mmol/L), hypertension (systolic blood pressure ≥130 mm Hg, or diastolic blood pressure ≥85 mm Hg), and high non-fasting glucose (≥5.6 mmol/L).

^ Additionally adjusted for time since last meal (<3, 3-5, ≥5 hours).

Supplemental table 3. Hazard ratio (HR) with 95% confidence interval for incident gastric adenocarcinoma related to metabolic syndrome with first two year follow up excluded.

Exposure	Total			Women			Men		
	No.	HR [†]	HR [‡]	No.	HR [†]	HR [§]	No.	HR [†]	HR [§]
Metabolic syndrome#									
No	127	1.0	1.0	53	1.0	1.0	74	1.0	1.0
Yes	156	1.23 (0.94-1.62)	1.73 (1.17-2.56)	60	1.17 (0.80-1.73)	1.41 (0.86-2.32)	96	1.35 (0.99-1.83)	1.28 (0.91-1.80)
Waist circumference									
Men<94 cm, women<80 cm	86	1.0	1.0	30	1.0	1.0	56	1.0	1.0
Men≥94 cm, women≥80 cm	197	1.40 (1.04-1.88)	2.14 (1.36-3.36)	83	1.29 (0.85-1.98)	1.86 (1.03-3.38)	114	1.55 (1.19-2.13)	1.31 (0.91-1.90)
HDL									
Men≥1.0 mmol/L, women≥1.3 mmol/L	217	1.0	1.0	89	1.0	1.0	128	1.0	1.0
Men<1.0 mmol/L, women<1.3 mmol/L	62	1.08 (0.78-1.50)	1.06 (0.70-1.60)	24	0.72 (0.46-1.27)	0.68 (0.39-1.63)	38	1.46 (1.01-2.10)	1.36 (0.93-1.97)
Triglycerides									
<1.7 mmol/L	170	1.0	1.0	80	1.0	1.0	90	1.0	1.0
≥1.7 mmol/L	111	0.86 (0.65-1.14)	0.96 (0.67-1.37)	33	0.70 (0.46-1.06)	0.61 (0.37-1.00)	78	0.98 (0.73-1.33)	0.90 (0.66-1.24)
Hypertension^α									
No	57	1.0	1.0	23	1.0	1.0	34	1.0	1.0
Yes	226	1.74 (1.21-2.50)	1.65 (1.04-2.64)	90	2.19 (1.32-3.64)	2.77 (1.49-5.15)	136	1.39 (0.95-2.04)	1.36 (0.92-2.02)
Non-fasting glucose[^]									
<5.6 mmol/L	131	1.0	1.0	50	1.0	1.0	81	1.0	1.0
≥5.6 mmol/L	152	1.43 (1.09-1.88)	1.96 (1.35-2.84)	63	1.58 (1.08-2.30)	1.85 (1.17-2.92)	89	1.16 (0.86-1.58)	1.21 (0.88-1.66)

[†] Adjusted for age (<60, ≥60 years).

[‡] Adjusted for age (<60, ≥60 years), sex (women, men), BMI (<25, 25-30, ≥ 30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes); family cancer history (no, yes).

[§] Adjusted to age (<60, ≥60 years), BMI (<25, 25-30, ≥ 30 kg/m²), education (primary/secondary school, high school, university), smoking status (no, yes); family cancer history (no, yes).

Metabolic syndrome was defined by the presence of ≥ 3 of following 5 factors: increased waist circumference (men ≥ 94 cm, women ≥ 80 cm), elevated triglycerides (≥ 1.7 mmol/L), low HDL (men < 1.0 mmol/L, women < 1.3 mmol/L), hypertension (systolic blood pressure ≥ 130 mm Hg, or diastolic blood pressure ≥ 85 mm Hg), and high non-fasting glucose (≥ 5.6 mmol/L).

^ Additionally adjusted for time since last meal (< 3 , 3-5, ≥ 5 hours).