Erichsen, R., Horvath-Puho, E., Lund, J. L., Dellon, E., Shaheen, N., Pedersen, L., ... Sorensen, H. (2017). Mortality and cardiovascular diseases risk in patients with Barrett's oesophagus: a population-based nationwide cohort study. *Alimentary Pharmacology and Therapeutics*, *45*(7), 973–982. https://doi.org/10.1111/apt.13962

Mortality and Cardiovascular Diseases Risk in Patients with Barrett's Esophagus: A population-based nationwide cohort study

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Short title: Barrett's esophagus and mortality

Abbreviations: CCI: Charlson Comorbidity Index; ICD: International Classification of Diseases; SNOMED: Systemized Nomenclature of Medicine

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Conflicts of interest: None

Authorship statement: RE is guarantor of the manuscript. RE, HTS, and JLL designed the study. LP and EHP were responsible for acquiring the data and conducting the analysis. RE drafted the first version of the manuscript and all authors contributed to the interpretation of the findings and the critical revision of the

manuscript for intellectual content. RE had full access to all the data in the study and had final responsibility to submit for publication. All authors have approved the final version of the manuscript, including the authorship list.

Word count: 3,045 (excluding abstract, tables, figure, and references)

Key words: Barrett's esophagus; cardiovascular disease; mortality

Abstract

Background: Patients with Barrett's esophagus may be at increased risk of mortality overall, and cardiovascular disease has been suggested as the main underlying cause of death.

Aim: To examine cause-specific mortality and risk of cardiovascular events among patients with Barrett's esophagus.

Methods: Utilizing existing Danish data sources (1997-2011), we identified all patients with histologically verified Barrett's esophagus (n=13,435) and 123,526 members of the general population matched by age, sex, and individual comorbidities. We calculated cause-specific mortality rates and incidence rates of cardiovascular diseases. We then compared rates between patients with Barrett's esophagus and the general population comparison cohort, using stratified Cox proportional hazard regression.

Results: Patients with Barrett's esophagus had a 71% increased risk of overall mortality. The cause-specific mortality rate per 1,000 person-years for patients with Barrett's esophagus was 8.5 for cardiovascular diseases, 14.7 for non-esophageal cancers, and 5.4 for esophageal cancer. Compared to the general population cohort, corresponding hazard ratios were 1.26 (95% confidence interval (CI): 1.15-1.38), 1.77 (95% CI: 1.65-1.90), and 19.4 (95% CI: 16.1-23.4), respectively. The incidence rates of cardiovascular diseases per 1,000 person-years for Barrett's esophagus patients and for persons from the general population cohort, respectively, varied from 0.4 and 0.2 for subarachnoid bleeding (hazard ratio 1.10, 95% CI: 0.87-1.39) to 8.1 and 5.9 for congestive heart failure (hazard ratio 1.33, 95% CI: 1.21-1.46).

Conclusion: Prophylactic measures targeted at cardiovascular diseases and non-esophageal cancers potentially could be more important than measures against esophageal cancer for improving prognosis among patients with Barrett's esophagus.

Introduction

Barrett's esophagus is a premalignant condition of the distal esophagus characterized by replacement of normal squamous epithelium with columnar epithelium.[1] Several recent studies have indicated that patients with Barrett's esophagus have higher mortality than the general population, but that death due to esophageal malignancy is not the primary underlying cause.[2-5] This is consistent with the finding that the annual malignant transformation rate in Barrett's esophagus is approximately 0.2%.[6-8] Evidence from different settings has indicated that cardiovascular diseases are the predominant underlying cause of death among patients with Barrett's esophagus, probably partially exacerbated by shared risk factors such as obesity, smoking, and alcohol consumption.[2, 3, 9-11] Given these findings, prophylactic screening for and treatment of cardiovascular diseases might be effective in patients with Barrett's esophagus, and healthcare expenditures better utilized on prevention of cardiovascular diseases than on regular follow-up endoscopies to detect the rare event of esophageal cancer. However, only sparse and conflicting population-based evidence exists on mortality in patients with Barrett's esophagus.[2, 12-14] Furthermore, studies of causes of death, including cardiovascular death, are generally susceptible to misclassification. Thus there is a need for assesment of the association between Barrett's esophagus and cardiovascular events.[15, 16] In this context, we utilized a nationwide population-based cohort of histologically verified Barrett's esophagus patients[6] first to examine overall and cause-specific mortality among patients with this condition and second to estimate their risk of cardiovascular events.

Materials and Methods

We conducted this matched cohort study in the setting of the entire Danish population. During the study period (January 1, 1997 - December 31, 2011), the cumulative population numbered 6,849,900 people. Individual-level data were linked using the unique 10-digit personal identifier assigned at birth or upon immigration to all Danish residents by the Danish Civil Registration System.[17]

Barrett's esophagus cohort

We used the Danish Pathology Registry to identify a cohort consisting of all Danish patients with histologically verified Barrett's esophagus during the 1997-2011 period.[6, 18] Since January 1, 1997, this Registry has recorded data on all pathology examinations conducted in Denmark, including date of examination, unique ID number of the specimen, the pathology department code, and diagnosis based on the Danish Systemized Nomenclature of Medicine (SNOMED) codes. Patients joined the cohort on the date of their first diagnosis of Barrett's esophagus (index date). (See Supplementary Table s1 for diagnosis codes.) We excluded patients with a previous diagnosis of myocardial infarction, stroke, venous thromboembolism, or heart failure, as these diseases comprised secondary study endpoints. Patients with Barrett's esophagus were categorized in a time-varying manner according to severity of histology, *i.e*., low-grade dysplasia, high-grade dysplasia, and esophageal cancer. We lacked information on the endoscopic appearance of the esophagus or the length of Barrett's lesions.

Population comparison cohort

We used the Danish Civil Registration System[19] to match each patient with Barrett's esophagus with 10 persons from the general population who were alive and without a Barrett's esophagus diagnosis on the corresponding patient's diagnosis date (index date). Matching criteria were age (5-year intervals), sex, and the individual conditions included in the Charlson Comorbidity Index (CCI) . We applied the same exclusion criteria to the comparison cohort as for the Barrett's cohort. In the event that an individual from the

comparison cohort developed Barrett's esophagus during the study period, follow-up time was terminated and the individual joined the Barrett's cohort.

Study endpoints

Our primary endpoint was mortality, with information on date of death obtained from the Civil Registration System.[19] We ascertained causes of death from the Danish Causes of Death Registry, which has recorded all deaths in Denmark since 1970.[15] This Registry codes causes of death according to *International Classification of Diseases, Tenth Revision* (ICD-10) codes. We categorized patients according to their underlying cause of death, *i.e*., neoplasms overall, non-esophageal cancer, esophageal cancer, circulatory system conditions, respiratory system conditions, digestive system conditions, all other causes, and unknown causes. (See Supplementary Table s1 for codes.) We also subcategorized causes of cancer deaths by specific cancer site.

Secondary endpoints were cardiovascular events, defined as a first-time diagnosis code of myocardial infarction, stroke, venous thromboembolism, or heart failure. (See Supplementary Table s1 for codes.) We obtained relevant data from the Danish National Patient Registry[20] which has tracked all non-psychiatric hospitalizations in Denmark since 1977 and outpatient hospital contacts since 1995. The Danish National Patient Registry records dates of admission and discharge and up to 20 discharge diagnoses, coded by physicians according to ICD codes (ICD-8 until the end of 1993 and ICD-10 thereafter).

Comorbidity

We defined comorbidities according to the diagnoses included in the CCI, as recorded in the Danish National Patient Registry.[21] The CCI assigns weights between one and six to a range of conditions. (See Supplementary Table s2). The conditions included in the CCI were not only considered individually for matching and analysis, but also as the components of a summed aggregate score that we classified as follows: score of 0 (no comorbidity), score of 1 (low comorbidity), and score 2 or more (high comorbidity).

In addition to the conditions in the CCI, we included information on prior diagnoses of atrial fibrillation/flutter, obesity, hypertension, and alcoholism. (See Supplementary Table s1 for codes.)

Statistical analyses

Barrett's patients and members of the population comparison cohort were followed from index date until endpoint date, emigration, or end of the study, whichever came first. We calculated mortality rates and incidence rates of cardiovascular diseases as the number of events divided by follow-up time. We used stratified Cox proportional hazard models to compute hazard ratios of mortality and cardiovascular events, comparing patients in the Barrett's cohort to individuals in the general population cohort. We computed hazard ratios for the first year of follow-up and for the second and subsequent years of follow-up separately to examine short-term vs. long-term mortality/risks. We also conducted an analysis excluding patients diagnosed with esophageal cancer up to 30 days after the index date.

We controlled for differences in age, sex, and comorbidity through matching and additionally adjusted for atrial fibrillation, hypertension, obesity, and alcoholism. In further analyses we did not adjust for atrial fibrillation and hypertension, since these factors may be intermediate factors along the causal pathway for the association of interest. In a time-varying analysis, we estimated mortality and risk of cardiovascular diseases by the histological severity of Barrett's esophagus according to the following categories: no dysplasia, low-grade dysplasia, high-grade dysplasia, and cancer. Patients contributed risk-time according to the histological severity of their Barrett's lesions at the beginning of follow-up and changed to a new category only in the event of increasing histological severity. To conduct this analysis, we dissolved the matching and adjusted for the matching factors.

In a subsequent analysis conducted to reduce bias due to uncontrolled confounding by lifestyle factors, we examined the relation between Barrett's esophagus and mortality and cardiovascular events among subgroups of patients with diagnoses of chronic obstructive pulmonary disease (surrogate for smoking) or alcoholism.

Results

We identified 13,427 patients with Barrett's esophagus and 123,526 persons from the general population, matched by age, gender, year of index date, and individual conditions in the CCI. Because we were unable to match all patients with Barrett's esophagus to 10 persons from the general population, small differences occurred between the characteristics of the Barrett's esophagus cohort and the general population comparison cohort (Table 1). Among patients with Barrett's esophagus and members of the general population cohort, median age on the diagnosis/index date was 61 and 60 years, respectively, and average follow-up was 4 and 5 years, respectively. The vast majority (>80%) of patients with Barrett's esophagus did not have dysplasia at diagnosis or during the course of follow-up.

Mortality

Patients with Barrett's esophagus generally had higher rate of mortality than subjects in the matched general population cohort (Figure 1 and Table 2). The overall mortality rate was 46.7 per 1,000 person-years among patients with Barrett's esophagus and 27.2 per 1,000 person-years among subjects from the general population cohort, corresponding to an adjusted hazard ratio of 1.71 (95% CI: 1.64-1.78). The hazard ratio was nearly 3.2-fold increased in the first year of follow-up, but only 1.4-fold increased in the second and subsequent years of follow-up. For patients with Barrett's esophagus, the highest mortality rates were associated with non-esophageal cancer and diseases of the circulatory system. These two causes of deaths also were associated with the highest mortality rates in the general population cohort, although to a lesser degree (Table 2). The mortality rate for esophageal cancer was the third highest among all causes of death for patients with Barrett's esophagus (disregarding the category of 'all other causes'), while among subjects in the general population cohort, esophageal cancer had the lowest rate of all major causes of deaths. In a subanalysis, Barrett's esophagus patients with known esophageal cancer were excluded as of the Barrett's esophagus diagnosis date (Supplementary Table S3). In this subanalysis, the mortality rate

for esophageal cancer decreased from 5.4 to 2.1 per 1,000 person-years among Barrett's patients, and esophageal cancer was associated with the lowest mortality rate of the major causes of death in this group.

Generally, the hazard ratios comparing cause-specific mortality among patients with Barrett's esophagus and members of the general population cohort were increased. This was most pronounced for esophageal cancer even when we excluded patients with known esophageal cancer at diagnosis and diseases of the digestive system (Table 2 and Supplementary Table S3). When we calculated hazard ratios without adjusting for atrial fibrillation and hypertension, the results did not change (not shown). Among non-esophageal cancers, malignancies of the stomach, colorectum, lungs and thorax, and lymphoid, hematopoietic and other sites had the highest rates (Table 3).

When Barrett's esophagus was evaluated by histological severity, the overall mortality rate increased with increasing histological severity. This pattern also was observed for mortality caused by neoplasia, particularly esophageal cancer (Table 4). For esophageal cancer, the mortality rate was very low in the absence of dysplasia and for patients with low-grade dysplasia. It was only among Barrett's patients with esophageal cancer that the mortality rate associated with this cancer exceeded the mortality rate associated with diseases of the circulatory system. We had too few observations to support an analysis of specific malignant causes of death according to severity of Barrett's esophagus. When we evaluated deaths caused by diseases of the circulatory, respiratory, and digestive system, the mortality rates did not change substantially by severity of Barrett's esophagus and the mortality rate ratios were only modestly increased.

Cardiovascular diseases

Table 5 displays the incidence rates and hazard ratios showing the association between Barrett's esophagus and different secondary endpoints. In general, patients with Barrett's esophagus were at modestly increased risk of cardiovascular diseases compared to individuals in the general population cohort. Hazard

ratios for secondary endpoints were very similar when the first year was compared to the second and subsequent years of follow-up, with the exception of risk of venous thromboembolism. Compared with the risks in the general population cohort, the risk of venous thromboembolism was 3.1-fold increased in the first year of follow-up and 1.4-fold increased in the second and subsequent years among Barrett's esophagus patients. We found no substantial changes in risk of cardiovascular disease by histological severity of Barrett's esophagus, although the risks appeared to increase slightly with increasing severity (Supplementary Table S4).

Smoking and alcoholism

Supplementary Tables S5 shows hazard ratios of mortality and cardiovascular events within subgroups of Barrett's esophagus patients with chronic obstructive pulmonary disease (surrogate for smoking) and alcoholism, compared to the general population cohort. The hazard ratios were attenuated towards the null for mortality and a few cardiovascular events. This might indicate some residual confounding by smoking and alcohol intake in the overall analysis.

Discussion

In this nationwide population-based cohort study of patients with histologically verified Barrett's esophagus, we found that overall mortality was 3.2-fold increased in the first year after diagnosis and 1.4-fold increased in the second and subsequent years, compared with an age-, sex-, and comorbidity- matched general population cohort. Cause-specific mortality rates in the Barrett's esophagus cohort were highest for non-esophageal cancers and for cardiovascular diseases, followed by esophageal cancer. When patients with known esophageal cancer on the date of their Barrett's esophagus diagnosis were excluded from the analysis, the mortality attributable to esophageal cancer was the lowest of the major causes of death among both the Barrett's esophagus and general population cohorts. For non-esophageal cancers, several malignancies contributed to the high cancer mortality rate among Barrett's esophagus patients. The histological severity of Barrett's esophagus impacted mortality caused by neoplasia overall, but affected mortality from other causes only slightly. We observed a modestly increased risk of cardiovascular events among Barrett's esophagus patients, which was not substantially impacted by the histological severity of Barrett's esophagus. The incidence rate of esophageal adenocarcinoma within our cohort of patients with Barrett's esophagus has previously been shown to be 1.2 (95% CI: 0.9-1.5) per 1000 person-years.[6]

Our findings of increased overall mortality compared to the general population are supported by a recent population-based study utilizing data from UK's Clinical Practice Research Datalink.[2] That study excluded deaths in the first year of follow-up and relied on Barrett's diagnoses from general practitioners rather than histologically verified diagnoses. Using individuals without Barrett's esophagus as the comparison group, the study reported a mortality ratio of 1.21 (95% CI: 1.14-1.30), after adjusting for sex, age at diagnosis, smoking, alcohol consumption, and body mass index. The study was an extension of a previous report by the same group and used the same data sources.[12] Its findings accord with at least five non-population-based studies.[5,9, 10, 22, 23] In contrast to the present study, the UK study[2] did not report an increased risk of cardiovascular death among patients with Barrett's esophagus. However, it did find that diseases of the

circulatory system, followed by non-esophageal neoplasms, were the major underlying causes of death among patients with Barrett's esophagus.

Our study did not include data on treatment of Barrett's esophagus. However, endoscopic ablative therapy was uncommon in our cohort during the study period. Our findings on causes of death are consistent with those of a recently published study including 4,982 patients treated with radiofrequency ablation of Barrrett's esophagus in the US.[11] In that study, the most common causes of death were non-esophageal cancers and cardiovascular diseases.

For unclear reasons, two previous population-based studies[13, 14] found no increase in overall mortality for patients with Barrett's esophagus compared to the general population. An analysis[13] based on the Netherlands Cohort Study found an observed-to-expected ratio of overall mortality of 1.1 (95% CI: 0.9-1.2) after accounting for differences in age and sex, and a study[14] conducted in Northern Ireland reported an age-standardized mortality ratio of 0.96 (95% CI: 0.84-1.07).

The current study extends existing evidence on mortality through its precise estimates and long-term follow-up of a large, nationwide cohort of patients with histologically verified Barrett's esophagus. Our study also accounted for coexisting diseases and provided estimates according to histological severity. In addition, the study is the first to examine the specific association between Barrett's esophagus and cardiovascular diseases. Such evidence is needed to foster an understanding of the possible increased risk of cardiovascular death among patients with Barrett's esophagus and also to evaluate whether patients with Barrett's esophagus should be offered cardiovascular screening or prophylactic treatment. Most, but not all, studies seem to agree that cardiovascular diseases are among the most frequent causes of death among patients with Barrett's esophagus.[2, 3, 9, 10] We also found high mortality related to non-esophageal cancers. Our findings, together with those of earlier studies, suggests that prophylactic measures against cardiovascular diseases and appropriate screening for non-esophageal cancers potentially could be even more important for improving the prognosis of patients with Barrett's esophagus, than prophylactic

measures against esophageal cancer, including surveillance endoscopy. This is especially true when one considers the questionable effectiveness of surveillance endoscopy in preventing death from esophageal adenocarcinoma.[24]

A previous population-based study reported a decreased risk of stroke death among patients with Barrett's esophagus. It speculated that individuals with low vascular tone, and hence low blood pressure and stroke risk, also have disturbed esophageal motor function, leading to gastroesophageal reflux and development of Barrett's esophagus.[14] However, our study did not confirm a decreased risk of stroke. It is also important to note that patients with Barrett's esophagus have been reported to have a high prevalence of hypertension.[25] An inverse association between Barrett's esophagus and stroke death based on a mechanism of decreased vascular tone/hypotension[13] therefore seems unlikely.

Study strengths include its population-based cohort design and a setting that provides equal and free access to healthcare, essentially eliminating referral bias. Complete follow-up of all patients prevented selection bias due to drop-out. In addition, we included only histologically verified diagnoses of Barrett's esophagus and therefore limited biases stemming from exposure misclassification. Finally, we were able to include a population comparison cohort matched to the Barrett's cohort on age, gender, and all conditions included in the Charlson Comorbidity Index.

Our study also had several limitations. Among these, residual confounding from smoking, obesity, and alcohol consumption is a serious concern, as indicated by the analyses within subgroups of individuals with chronic obstructive pulmonary disease or alcoholism. Our findings also may have been influenced by unknown confounding and by misclassification. Although it is generally accepted that a diagnosis of Barrett's esophagus should rely on the correlation between endoscopic and pathologic findings[25], we used only pathological findings. It is therefore possible that cases of cardia intestinal metaplasia or ultrashort (< 1cm) Barrett's esophagus were included, although international guidelines advise against taking routine

biopsies from the distal esophagus in the absence of endoscopic signs of Barrett's esophagus.[27] Although misclassification of our primary outcome (death) seems unlikely, it is well known that causes of death may be misclassified.[15, 16] We also cannot rule out misclassification of the secondary endpoints, cardiovascular events. Finally, since guidelines recommend regular follow-up of patients with Barrett's esophagus, our findings may be influenced by surveillance bias.

In conclusion, we found that patients with Barrett's esophagus were at 71% increased risk of overall mortality, and non-esophageal cancers and cardiovascular diseases were the main underlying causes of death. In addition, the rate of cardiovascular diseases was increased. Prophylactic measures against cardiovascular diseases and appropriate screening for non-esophageal cancers potentially could be even more important for improving prognosis in patients with Barrett's esophagus than preventive measures against esophageal cancer, including surveillance endoscopy.

Table 1. Characteristics of patients with Barrett's esophagus and a matched general population cohort[a], Denmark 1997-2011.

	Patients with Barrett's esophagus		Matched general population cohort [a]	
	Number	**(%)**	**Number**	**(%)**
Total	13,427	100.0	123,526	100.0
Women	4,682	34.9	43,676	35.4
Men	8,745	65.1	79,850	64.6
Age at index date				
<49	2,827	21.1	27,779	22.5
50-69	6,839	51.9	63,718	51.6
70+	3,761	28.0	32,029	25.9
Year of index date				
1997-2001	3,323	24.7	31,075	25.2
2002-2006	4,612	34.3	42,669	34.5
2007-2011	5,492	40.9	49,782	40.3
Comorbidities				
CCI score = 0	9,750	72.6	92,780	75.1
CCI score = 1	1,957	14.6	16,842	13.6
CCI score = 2+	1,720	12.8	13,904	11.3
Alcoholism	722	5.4	2,280	1.8
Obesity	260	1.9	1,494	1.2
Hypertension	1,214	9.0	6,982	5.7
AFLI/AFLA	381	2.8	2,493	2.0
Dysplasia/neoplasia[b]				
No dysplasia	10,843	80.8	N/A	-
Low-grade dysplasia	1,086	8.1	N/A	-
High-grade dysplasia	821	6.1	N/A	-
Esophageal cancer	677	5.0	256	0.2

Abbreviations: AFLI/AFLA: Atrial fibrillation/flutter; CCI: Charlson's Comorbidity Index

[a] Matching criteria were age (5-year intervals), gender, year of index date, and comorbidity as defined by the Charlson's Comorbidity Index.

[b]According to the most severe degree of dysplasia/neoplasia during follow-up.

Table 2. Overall and cause-specific mortality among patients with Barrett's esophagus and a matched general population cohort [a], Denmark, 1997-2011.

Major causes of death (ICD-10 codes)	N	Person-years	Rate per 1000 person-years	Unadjusted HR	Adjusted HR	Adjusted HR <1 year	Adjusted HR 1-15 years
Overall mortality							
Barrett´s esophagus	3,284	70,335	46.7 (45.1 - 48.3)	1.77 (1.70-1.84)	1.71 (1.64-1.77)	3.19 (2.95-3.44)	1.41 (1.34-1.48)
Population cohort[a]	19,521	718,912	27.2 (26.8 - 27.5)	Ref.	Ref.	Ref.	Ref.
Neoplasms overall							
Barrett´s esophagus	1,416	70,335	20.1 (19.1 - 21.2)	2.39 (2.25-2.55)	2.37 (2.23-2.52)	5.52 (4.97-6.13)	1.63 (1.51-1.77)
Population cohort[a]	6,381	718,912	8.9 (8.7 - 9.1)	Ref.	Ref.	Ref.	Ref.
Neoplasm without esophageal cancer							
Barrett´s esophagus	1,037	70,335	14.7 (13.9 - 15.7)	1.79 (1.67-1.92)	1.77 (1.65-1.90)	3.89 (3.46-4.39)	1.28 (1.18-1.40)
Population cohort[a]	6,175	718,912	8.6 (8.4 - 8.8)	Ref.	Ref.	Ref.	Ref.
Esophageal cancer							
Barrett´s esophagus	379	70,335	5.4 (4.9 - 5.9)	19.2 (16.0-23.1)	19.4 (16.1-23.4)	43.3 (30.4-61.7)	12.2 (9.67-15.4)
Population cohort[a]	206	718,912	0.3 (0.2 - 0.3)	Ref.	Ref.	Ref.	Ref.
Circulatory system							
Barrett´s esophagus	598	70,335	8.5 (7.8 - 9.2)	1.31 (1.20-1.44)	1.26 (1.15-1.38)	1.26 (0.99-1.59)	1.26 (1.14-1.39)
Population cohort[a]	4,753	718,912	6.6 (6.4 - 6.8)	Ref.	Ref.	Ref.	Ref.
Respiratory system							
Barrett´s esophagus	272	70,335	3.9 (3.4 - 4.3)	1.22 (1.07-1.39)	1.18 (1.04-1.36)	1.40 (1.03-1.91)	1.15 (0.99-1.33)
Population cohort[a]	2,177	718,912	3.0 (2.9 - 3.2)	Ref.	Ref.	Ref.	Ref.
Digestive system							
Barrett´s esophagus	307	70,335	4.4 (3.9 - 4.9)	2.60 (2.27-2.97)	2.40 (2.09-2.75)	4.15 (3.22-5.36)	1.97 (1.67-2.33)
Population cohort[a]	1,211	718,912	1.7 (1.6 - 1.8)	Ref.	Ref.	Ref.	Ref.
All other causes							
Barrett´s esophagus	668	70,335	9.5 (8.8 - 10.2)	1.49 (1.37-1.63)	1.41 (1.30-1.54)	1.96 (1.60-2.38)	1.32 (1.20-1.45)
Population cohort[a]	4,663	718,912	6.5 (6.3 - 6.7)	Ref.	Ref.	Ref.	Ref.
Unknown causes of death							
Barrett´s esophagus	23	70,335	0.3 (0.2 - 0.5)	0.70 (0.46-1.08)	0.71 (0.46-1.09)	1.31 (0.62-2.80)	0.57 (0.34-0.96)
Population cohort[a]	336	718,912	0.5 (0.4 - 0.5)	Ref.	Ref.	Ref.	Ref.

Numbers in parentheses are 95% confidence intervals.

[a] Matching criteria were age (5-year intervals), gender, year of index date, and comorbidity as defined by the Charlson Comorbidity Index.

Table 3. Mortality caused by malignancies among patients with Barrett's esophagus and a matched general population cohort [a], Denmark, 1997-2011.

Major malignant causes of death (ICD-10 codes)	N	Person-years	Rate per 1000 person-years	Unadjusted HR	Adjusted HR	Adjusted HR <1 year	Adjusted HR 1-15 years
Oral and pharynx (C00-C14)							
Barrett´s esophagus	22	70,335	0.3 (0.2 - 0.5)	1.59 (0.99-2.55)	1.33 (0.78-2.25)	0.56 (0.12-2.64)	1.54 (0.86-2.74)
Population cohort[a]	154	718,912	0.2 (0.2 - 0.2)	Ref.	Ref.	Ref.	Ref.
Digestive organs (C15-C26)							
Barrett´s esophagus	790	70,335	11.2 (10.5 - 12.0)	4.84 (4.43-5.30)	4.80 (4.39-5.26)	12.4 (10.6-14.5)	2.92 (2.60-3.29)
Population cohort[a]	1,759	718,912	2.4 (2.3 - 2.6)	Ref.	Ref.	Ref.	Ref.
Esophagus (C15)							
Barrett´s esophagus	379	70,335	5.4 (4.9 - 5.9)	19.2 (16.0-23.1)	19.2 (15.9-23.1)	40.6 (28.9-57.1)	12.2 (9.71-15.4)
Population cohort[a]	206	718,912	0.3 (0.2 - 0.3)	Ref.	Ref.	Ref.	Ref.
Stomach (C16)							
Barrett´s esophagus	154	70,335	2.2 (1.9 - 2.5)	8.45 (6.71-10.6)	8.49 (6.74-10.7)	16.8 (11.5-24.6)	5.42 (4.00-7.33)
Population cohort[a]	188	718,912	0.3 (0.2 - 0.3)	Ref.	Ref.	Ref.	Ref.
Colorectum and anus (C18-C21)							
Barrett´s esophagus	131	70,335	1.9 (1.6 - 2.2)	1.67 (1.37-2.02)	1.64 (1.35-1.99)	3.81 (2.71-5.35)	1.19 (0.93-1.52)
Population cohort[a]	844	718,912	1.2 (1.1 - 1.3)	Ref.	Ref.	Ref.	Ref.
Hepatobiliary system (C22-C24)							
Barrett´s esophagus	42	70,335	0.6 (0.4 - 0.8)	2.33 (1.63-3.32)	2.29 (1.60-3.26)	7.48 (4.31-13.0)	1.06 (0.63-1.79)
Population cohort[a]	180	718,912	0.3 (0.2 - 0.3)	Ref.	Ref.	Ref.	Ref.
Pancreas (C25)							
Barrett´s esophagus	71	70,335	1.0 (0.8 - 1.3)	2.36 (1.81-3.09)	2.33 (1.78-3.05)	6.66 (4.28-10.4)	1.37 (0.95-1.98)
Population cohort[a]	311	718,912	0.4 (0.4 - 0.5)	Ref.	Ref.	Ref.	Ref.
Lung and thorax (C30-C39)							
Barrett´s esophagus	201	70,335	2.9 (2.5 - 3.3)	1.32 (1.13-1.53)	1.28 (1.10-1.49)	2.39 (1.81-3.15)	1.04 (0.86-1.25)
Population cohort[a]	1,587	718,912	2.2 (2.1 - 2.3)	Ref.	Ref.	Ref.	Ref.
Bones, connective tissue, and skin (C40-C49)							
Barrett´s esophagus	28	70,335	0.4 (0.3 - 0.6)	1.45 (0.96-2.18)	1.37 (0.90-2.09)	2.51 (1.21-5.22)	1.08 (0.64-1.82)
Population cohort[a]	220	718,912	0.3 (0.3 - 0.3)	Ref.	Ref.	Ref.	Ref.
Breast (C50)							
Barrett´s esophagus	50	70,335	0.7 (0.5 - 0.9)	1.94 (1.42-2.66)	1.95 (1.42-2.67)	2.69 (1.45-4.98)	1.77 (1.22-2.55)
Population cohort[a]	312	718,912	0.4 (0.4 - 0.5)	Ref.	Ref.	Ref.	Ref.
Genital organs (C51-C63)							
Barrett´s esophagus	91	70,335	1.3 (1.0 - 1.6)	1.04 (0.83-1.30)	1.02 (0.82-1.28)	1.66 (1.07-2.59)	0.89 (0.69-1.16)
Population cohort[a]	922	718,912	1.3 (1.2 - 1.4)	Ref.	Ref.	Ref.	Ref.

Kidney and urinary tract (C64-C68)							
Barrett´s esophagus	54	70,335	0.8 (0.6 - 1.0)	1.49 (1.11-2.01)	1.48 (1.10-1.99)	2.15 (1.22-3.82)	1.31 (0.92-1.85)
Population cohort[a]	417	718,912	0.6 (0.5 - 0.6)	Ref.	Ref.	Ref.	Ref.
Eyes and CNS (C69-C72)							
Barrett´s esophagus	14	70,335	0.2 (0.1 - 0.3)	1.00 (0.57-1.75)	0.97 (0.55-1.71)	2.29 (0.75-7.04)	0.79 (0.41-1.53)
Population cohort[a]	141	718,912	0.2 (0.2 - 0.2)	Ref.	Ref.	Ref.	Ref.
Endocrine glands (C73-C75)							
Barrett´s esophagus	1	70,335	0.0 (0.0 - 0.1)	0.60 (0.08-4.69)	0.58 (0.07-4.57)	4.27 (0.38-47.4)	N/A
Population cohort[a]	17	718,912	0.0 (0.0 - 0.0)	Ref.	Ref.	Ref.	Ref.
Lymphoid, hematopoietic and others (C76-C97)							
Barrett´s esophagus	145	70,335	2.1 (1.7 - 2.4)	2.06 (1.71-2.49)	2.05 (1.70-2.48)	5.57 (4.05-7.66)	1.33 (1.04-1.70)
Population cohort[a]	731	718,912	1.0 (0.9 - 1.1)	Ref.	Ref.	Ref.	Ref.

Numbers in parentheses are 95% confidence intervals.

[a] Matching criteria were age (5-year intervals), gender, year of index, and comorbidity as defined by the Charlson Comorbidity Index.

Table 4. Overall and cause-specific mortality according to degree of dysplasia and neoplasia in patients with Barrett's esophagus and in a matched general population cohort, Denmark, 1997-2011.

Major causes of death (ICD-10 codes)	Population Cohort[a]	No dysplasia		Low-grade dysplasia		High-grade dysplasia		Esophageal cancer	
	Mortality rates[a]	Mortality rates[a]	Adjusted hazard ratio[b]	Mortality rates[a]	Adjusted hazard ratio[b]	Mortality rates[a]	Adjusted hazard ratio[b]	Mortality rates[a]	Adjusted hazard ratio[b]
Overall mortality	27.2 (26.8-27.5)	38.3 (36.8-39.9)	1.40 (1.34-1.46)	51.2 (45.0-57.5)	1.43 (1.26-1.61)	69.2 (59.7-78.7)	1.79 (1.56-2.06)	345 (315-376)	10.0 (9.14-11.0)
Neoplasms overall	8.9 (8.7-9.1)	13.0 (12.1-13.9)	1.47 (1.37-1.59)	18.7 (15.0-22.5)	1.74 (1.42-2.13)	34.3 (27.6-41.0)	2.94 (2.41-3.58)	306 (277-335)	25.9 (23.4-28.5)
Neoplasms without esophageal cancer	8.6 (8.4-8.8)	12.3 (11.4-13.1)	1.44 (1.34-1.56)	17.0 (13.4- 20.5)	1.62 (1.31-2.01)	28.2 (22.1-34.2)	2.47 (1.98-3.07)	86.9 (71.5-102)	7.62 (6.37-9.13)
Esophageal cancer	0.3 (0.3-0.3)	0.7 (0.5-0.9)	2.41 (1.74-3.34)	1.8 (0.6-2.9)	5.45 (2.79-10.6)	6.1 (3.3- 8.9)	18.8 (11.6-30.5)	220 (195-244)	511 (425- 613)
Circulatory system	6.6 (6.4-6.8)	7.9 (7.2-8.6)	1.25 (1.14-1.37)	11.6 (8.7-14.6)	1.34 (1.04-1.74)	10.5 (6.8-14.2)	1.09 (0.76-1.55)	18.5 (11.4-25.7)	2.31 (1.57-3.41)
Respiratory system	3.0 (2.9-3.2)	3.5 (3.0-4.0)	1.19 (1.03-1.37)	6.7 (4.5-9.0)	1.70 (1.21-2.39)	5.4 (2.8- 8.1)	1.25 (0.76-2.05)	6.4 (2.2-10.6)	1.73 (0.90-3.34)
Digestive system	1.7 (1.6-1.8)	4.3 (3.8-4.9)	2.00 (1.74-2.29)	4.9 (3.0-6.9)	1.73 (1.16-2.57)	4.4 (2.0- 6.8)	1.71 (0.99-2.96)	3.6 (0.4-6.7)	1.61 (0.67-3.88)
All other causes	6.5 (6.3-6.7)	9.3 (8.6-10.1)	1.40 (1.28-1.52)	8.7 (6.1-11.2)	0.96 (0.71-1.29)	14.2 (9.9-18.6)	1.50 (1.10-2.03)	10.0 (4.8-15.2)	1.31 (0.78-2.21)
Unknown causes of death	0.5 (0.4-0.5)	0.3 (0.2-0.4)	0.65 (0.40-1.05)	0.6 (0.0-1.3)	1.05 (0.34-3.28)	0.3 (0.0- 1.0)	0.57 (0.08-4.06)	0.7 (0.0-2.1)	1.09 (0.15-7.79)

Numbers in parenthesis are 95% confidence intervals.

[a] Rates per 1000 person-years.

[b] Hazard ratios for the comparison of patients with Barrett's esophagus to a general population cohort, adjusted for age (5-year intervals), gender, year of index date, Charlson Comorbidity Index score, atrial fibrillation/flutter, obesity, hypertension, and alcoholism.

Table 5. Incidence rates and hazard ratios (HRs) of cardiovascular diseases in patients with Barrett's esophagus and a matched general population cohort[a], Denmark, 1997-2011.

Outcome	N	Person-years	Rate per 1000 person-years	Unadjusted HR	Adjusted HR	Adjusted HR <1 year	Adjusted HR 1-15 years
Myocardial infarction							
Barrett´s esophagus	366	69,064	5.3 (4.8 - 5.9)	1.11 (1.00-1.24)	1.10 (0.99-1.24)	1.12 (0.85-1.47)	1.10 (0.98-1.25)
Population cohort	3,374	707,852	4.8 (4.6 - 4.9)	Ref.	Ref.	Ref.	Ref.
Subarachnoid hemorrhage							
Barrett´s esophagus	25	70,228	0.4 (0.2 - 0.5)	1.38 (0.90-2.12)	1.29 (0.83-2.00)	1.54 (0.64-3.71)	1.21 (0.72-2.01)
Population cohort	174	718,182	0.2 (0.2 - 0.3)	Ref.	Ref.	Ref.	Ref.
Hemorrhagic stroke							
Barrett´s esophagus	85	70,135	1.2 (1.0 - 1.5)	1.18 (0.94-1.49)	1.10 (0.87-1.39)	0.78 (0.41-1.49)	1.17 (0.91-1.50)
Population cohort	756	717,085	1.1 (1.0 - 1.1)	Ref.	Ref.	Ref.	Ref.
Ischemic stroke							
Barrett´s esophagus	333	69,318	4.8 (4.3 - 5.3)	1.21 (1.08-1.36)	1.18 (1.05-1.33)	1.23 (0.92-1.64)	1.17 (1.03-1.33)
Population cohort	2,781	710,376	3.9 (3.8 - 4.1)	Ref.	Ref.	Ref.	Ref.
Venous thromboembolism							
Barrett´s esophagus	295	69,523	4.2 (3.8 - 4.7)	1.70 (1.50-1.93)	1.65 (1.46-1.88)	3.11 (2.40-4.03)	1.40 (1.21-1.62)
Population cohort	1,813	713,902	2.5 (2.4 - 2.7)	Ref.	Ref.	Ref.	Ref.
Congestive heart failure							
Barrett´s esophagus	555	68,860	8.1 (7.4 - 8.7)	1.37 (1.25-1.50)	1.33 (1.21-1.46)	1.53 (1.23-1.90)	1.29 (1.16-1.43)
Population cohort	4,171	708,087	5.9 (5.7 - 6.1)	Ref.	Ref.	Ref.	Ref.

Numbers in parentheses are 95% confidence intervals.

[a] Matching criteria were age (5-year intervals), gender, year of index, and comorbidity as defined by the Charlson Comorbidity Index.

Figure legend

Figure 1. Cumulative mortality curves for patients with Barrett's esophagus and a matched general population cohort, Denmark, 1997-2011.

Statement of interest:

1. **Authors' declaration of personal interests:** George Davey Smith works within a unit, The Medical Research Council Integrative Epidemiology Unit at the University of Bristol, which is supported by the Medical Research Council (MC_UU_12013/1) and the University of Bristol.
2. **Declaration of funding interests:** This study was supported by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation, and the Aarhus University Research Foundation.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract X
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found X
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported X
Objectives	3	State specific objectives, including any prespecified hypotheses X
Methods		
Study design	4	Present key elements of study design early in the paper X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection X
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up X
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group X
Bias	9	Describe any efforts to address potential sources of bias X
Study size	10	Explain how the study size was arrived at X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why X
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding X
		(*b*) Describe any methods used to examine subgroups and interactions X
		(*c*) Explain how missing data were addressed X
		(*d*) If applicable, explain how loss to follow-up was addressed X

		(*e*) Describe any sensitivity analyses X
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed X
		(b) Give reasons for non-participation at each stage X
		(c) Consider use of a flow diagram X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders X
		(b) Indicate number of participants with missing data for each variable of interest X
		(c) Summarise follow-up time (eg, average and total amount) X
Outcome data	15*	Report numbers of outcome events or summary measures over time X
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included X
		(*b*) Report category boundaries when continuous variables were categorized X
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period X
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses X
Discussion		
Key results	18	Summarise key results with reference to study objectives X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence X
Generalisability	21	Discuss the generalisability (external validity) of the study results X
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based X

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.