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Original article

Mortality risk increased in colonic diverticular disease: a nationwide cohort study

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ABSTRACT

Introduction: There are limited population cohort data on overall and cause-specific mortality in colonic diverticular disease.

Objective: To measure overall and cause-specific mortality in colonic diverticular disease, compared to matched reference individuals and siblings.

Methods: Population-based cohort study ("the ESPRESSO study") in Sweden. There were 97,850 cases with a medical diagnosis of diverticular disease (defined by international classification of disease codes) and colorectal histology identified in 1987–2017 from histopathology reports. The mortality risk between individuals with colonic diverticular disease and matched reference individuals (n = 453/634) from the general population was determined. Cox regression models adjusted for comorbidity estimated hazard ratios (HRs) for all-cause mortality.

Abbreviations: aHR, Adjusted hazard ratio; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; CVD, Cardiovascular disease; ESPRESSO, Epidemiology strengthened by histopathology reports in sweden; FIT, Fecal immunochemical test; HR, Hazard ratio; IBD, Inflammatory bowel disease; ICD, International Classification of Disease; IQR, Interquartile Range; PY, per year; SD, standard deviation; SNOMED, Systematized Nomenclature of Medicine; TPR, Total Population Register.

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Results: During follow-up, there were 32,959 deaths in individuals with colonic diverticular disease (44/1000 person-years) compared with 127,153 in matched reference individuals (34/1000 person-years), resulting in an HR of 1.27 (95%CI 1.25–1.29). Also compared to siblings, colonic diverticular disease patients were at increased risk of death, HR 1.39 (95%CI 1.33–1.45). Mortality risks were further increased in colonic diverticular disease patients with a colorectal biopsy showing any mucosal inflammation HR 1.36; (95%CI 1.33–1.38), with the most significant increase during the first year after diagnosis HR 2.18; (95%CI 2.05–2.32).
Conclusions: Mortality in colonic diverticular disease is increased over reference individuals in the general population. The presence of mucosal inflammation on colorectal biopsies is a predictor of increased risk of mortality.

Introduction

Colonic diverticulae are common but represent a mostly asymptomatic condition that affects an estimated 17.5% of the general population [1]. It is estimated that 30% of individuals aged 60 and over and 70% aged over 80 years in Westernized countries (U.S., Europe, and Australia [2–4]) have colonic diverticulosis. Of those, approximately 4% become symptomatic (and develop acute colonic diverticulitis [1]. Acutely, diverticular disease can often be managed by conservative treatments in an outpatient setting [5]. When further complications develop, such as perforation, abscess, stricture, obstruction, or fistulas, usually inpatient medical intervention is required [6]. Diverticular disease results in high direct and indirect economic costs and a high healthcare burden [7].

In Australia, 0.2% of all deaths were registered as having been attributed to diverticular disease, though at autopsy, 48% had diverticular disease incidentally identified [8]. The registered direct cause of mortality from diverticular disease is assigned to severe disease complications [9]. Hunt et al. recently reported that the current age-adjusted mortality rate for diverticular disease globally is 0.51 deaths per 100,000 colonic diverticular disease patients [10]. A recent Swedish study concluded that for patients that are admitted to a hospital for diverticulitis, long and short-term survival is significantly reduced [11]. Compared to diverticulitis-free patients, those with diverticulitis had a four times higher mortality rate within 100 days of admission (HR 4.44 (95% confidence interval 4.26–4.63)) [11].

There are relatively few studies that have addressed overall or cause-specific mortality in diverticular disease. Early literature assessed mortality risk in diverticular disease by gender differences [12], and other factors such as perforation [13,14], obesity [15,10], the role of progression from acute to complicated diverticular disease, [16], surgery complication outcomes [17], and hospitalization outcomes [11,18]. To the best of our knowledge no studies have been conducted to measure both cause-specific and overall mortality in a large nation-based cohort of individuals with diverticular disease, compared to reference individuals with matching covariates and comorbidities, and with familial cofounders considered in sibling analyses.

Therefore, in this retrospective cohort study, we aimed to identify whether diverticular disease increases the risk of cause-specific or overall mortality compared to those individuals without a diagnosis of diverticular disease. We further aimed to identify if inflammation in colorectal rectal biopsies obtained in the course of diverticular disease increased patient mortality risk compared to those with healthy mucosa. Siblings were included to determine potential genetic and early life environmental confounding.

Methods

In this retrospective cohort study, individuals with diverticular disease were linked to matched reference individuals from nationwide health registers, and we examined absolute and relative risks of death in diverticular disease.

Source population

Epidemiology Strengthened by histoPathology Reports in Sweden (ESPRESSO) study is a nationwide Swedish histopathology population-based cohort study that yielded 6.1 million gastrointestinal pathology reports, dating from 1965 to 2017 [1], assembled between 2015 and 2017, through histopathology data procurement from all pathology departments ($n = 28$) in Sweden [19].

All individuals identified from within the ESPRESSO cohort, with a recorded topographical code T67 -T68 (colorectal site histology), aged 18 years or over with a medical diagnosis of diverticular disease onward from 1987 (ICD-9 or ICD-10), were included in the study. Inpatient and outpatient data records were reviewed for Systematized Nomenclature of Medicine (SnoMed) characteristics for the International Classification of Disease (ICD) codes (ICD-8, ICD-9, ICD-10), relating to T67 and T68 (e*Table 1*). Patient register ICD codes in Sweden have a positive predictive value of 85%–95% [20].

Definition of diverticular disease

Diverticular disease for the purposes of this study was defined as any subject with hospital records identifying colonic diverticulae listed under the following ICD codes, ICD-8 (562,10; 562,11; 562,18; 562,19), ICD-9 (562B), ICD-10 (K57.2, K57.3, K57.4, K57.5, K57.8, K57.9) since 1987 in the Swedish Patient Register; as well as a SnoMed code relating to Topography (anatomical site) codes (T), T67-T68 (colorectal). Patients were subdivided into those with morphology codes, referring to histological features, that is, changes in cells and tissues, (M). These included records indicating recorded medical history of diverticulosis, diverticulitis, or a subgroup thereof, containing one or more colonic diverticulae (M327, M32700, M32710, M46400, M4642,) with acute, chronic, or unspecified inflammation in the colonic mucosa on histology (M40–44, M4000, M4100, M4211, M4300, M4502, and M4500) or normal appearance (M00100, M00110). The date of diverticular disease diagnosis was the second of either the first ICD code for diverticular disease or colorectal histology report (both conditions had to be fulfilled).

Inclusions and exclusions

The study cohort was restricted to individuals aged 18 years at the start of follow-up. Individuals with a previous record of (subtotal) colectomy; or who had emigrated at any point in their life, despite having histology in Sweden were excluded or censored. Individuals with pathology reports originating from surgery (as defined by the following codes: 4650, 4651, 4652, 4653, 4654, JFH00,

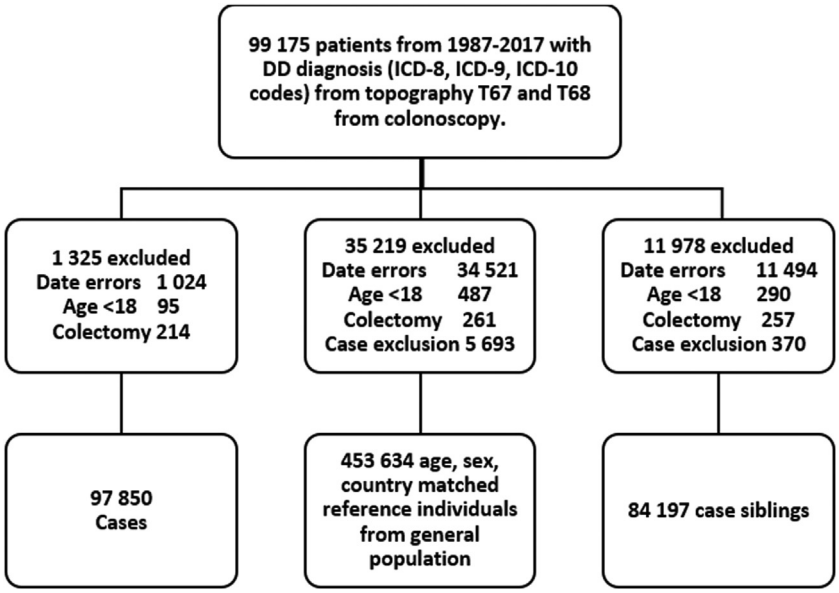

Fig. 1. A flowchart of identified patients with diverticular disease (DD) and their matched reference individuals and siblings from 1987 to 2017 with a diverticular disease diagnosis from topography t67 and t68, with exclusions.

JFH01, JFH11, JFH20, JFH30, JFH33, JFH40, or JFH96) were excluded from the study.

Covariates and comorbidities

Comorbidities for diverticular disease, matched reference individuals, and sibling cohorts included inflammatory bowel disease, respiratory disease, cardiovascular disease, cancer, diabetes mellitus, chronic obstructive pulmonary disease (COPD), obesity, and alcohol-related disease (*eTable 1*). Comorbidities diagnosed prior to the start of follow-up were obtained from the Swedish Patient Register and recorded. An earlier review has indicated a positive predictive value of 85%–95% for most diagnoses in this register [20]. Data on the country of birth (Nordic vs. not Nordic) was obtained from the Total Population Register [21], while data on education (4 categories: ≥9, 10–12, ≥13 years, and missing) were retrieved from the national LISA database [22].

Comparison group

Two groups were identified for comparison to the diseased cohort. The primary group included reference individuals from the Swedish general population identified through the Total Population Register (TPR) [23]. For each diverticular disease case, five reference individuals (n = 494/546) were matched by sex, age, calendar year, and location of residence from within the general population. Subjected to exclusion parameters 35,219 (7%) were excluded. Thirty-four of 521 (7%) due to date issues (typically a reference individual was matched on January 1 of a certain year, but the index patient may have been biopsied on June 1, and then one of the reference individuals had already died or emigrated and was excluded), 487 younger than 18 years, 261 colectomy, and 5/693 (1%) because the case they were matched to had been excluded. The primary reference individual cohort remaining was 453/634 (92%) (Fig. 1).

The secondary comparison group identified were full siblings of diverticular disease cases (n = 96/545), identified through the same Population Register. The sibling comparisons were naturally restricted to diverticular disease cases with siblings. Exclusion criteria parameters were also subjected to the siblings. Overall, 11/978 (12%) were excluded, 11/494 (12%) due to date errors, 290 (0%) for being under 18 years of age, 257 (0%) for colectomy, and 370 (0%) from matched case exclusion. The sibling cohort remaining is 84/197 (87%) (Fig. 1). The inclusion of siblings served the purpose of assessing the potential influence of shared environmental and genetic factors.

Mortality data

Data on overall death and date of death were obtained from the Swedish TPR. Cause-specific deaths were obtained from the Swedish Cause of Death Register [24].

Statistical analysis

All statistical analyses were performed using R version 4.0.5.

Baseline characteristics are described using numbers and percentages for categorical variables and mean (SD), median, and range for numerical variables.

The start of follow-up was defined as the date of histology, or the date of ICD code, whichever was entered last of the two parameters. End of follow-up was defined as: death or emigration during the study period; or end of the study, December 31, 2017. For reference individuals and siblings' follow-ups also ended with a diverticular disease diagnosis. Death numbers were characterized further by deaths within 30, 90, and 365 days, n (%).

To estimate the survival curve, Kaplan-Meier plots were analyzed. We examined all-cause mortality, and more specifically death from cardiovascular disease, cancer, respiratory disease, colorectal cancer, or other cause.

The primary endpoint, time to all-cause death, as well as secondary endpoints, time to cause-specific death, were analyzed using Cox proportional hazards models. For each of the endpoints, we first stratified by matched cohort (i.e., separate baseline hazard functions are fit for each stratum). We then adjusted for education, CVD, cancer, respiratory disease, and inflammatory bowel disease ("model II"). In a separate analysis, we also adjusted for diseases that might represent lifestyle factors: COPD, obesity, and alcohol-related disease ("model III").

Results are presented as Hazard ratios with 95% confidence intervals, as well as two-sided P-values. No adjustment for multiplic-

ity was performed and all *P*-values should be interpreted with that in mind.

In addition to analyzing the whole cohort, we also stratified for education level, covariates, and comorbidities, and carried out subanalyses among diverticular disease individuals with either inflammation/diverticula versus normal mucosa. The difference in mortality according to underlying histopathology was further tested through an interaction test.

Further sensitivity analyses were performed to evaluate the impact of other potential confounders. Parameters considered included the year of diagnosis and follow-up allowance, less than one year between histology and hospital code, diagnosis as inpatient or outpatient, exclusion of IBD, and gastrointestinal surgery within 30 days of diagnosis.

Ethics

This study was approved by the Stockholm Ethics Review Board (No. 2014/1287–31/4) on August 27, 2014. Informed consent was waived due to the registry-based nature of the study [25].

Results

There were 99,175 incident cases of diverticular disease from 1987 to 2017.

After exclusions, 97,850 (99%) of diverticular disease cases remained, which were matched to 453/634 reference individuals from the general population. A second comparative population was established from siblings of the cases (n = 84 197) (Fig. 1). The male to female ratio was matched between cases and reference individuals, (41/59%, 41/59% respectively), and the sibling ratio was 50/50 (Table 1). The median IQR for cases was age 65 years (55.0–74.0) at the time of diagnosis.

The number of cases is represented in a bar plot (*eFig. 1*) to show the number of cases over the study period.

A baseline description analysis was run for cases, reference individuals, and sibling characteristics for deaths occurring within 30, 90, and 365 days (*eTable 2*), of the follow-up time for exposures and deaths. The median follow-up time in years for the cases is 6.3 (IQR 3.3–10.7). Follow-up IQR for reference individuals and siblings were comparative. The cumulative mortality at 30 days after diverticular disease diagnosis was 1.6% (n = 1158), at 90 days 2.8% (n = 2776), and at 365 days 5.9% (n = 5733).

During the period of follow-up, there were 32,959 deaths in individuals with diverticular disease (44/1000 person-years) compared with 127 of 153 in matched reference individuals (34/1000 person-years), resulting in an HR of 1.27 (95%CI = 1.25–1.29).

The Kaplan-Meier plot figures for death over time, show the crude HR (95% CI) for causes of death for cases and reference individuals, up to 5 years and up to 15 years respectively (Figs. 2 and 3). Only 789 (2.4%) of all deaths had diverticulitis as the underlying cause of death.

Individually, death from colorectal cancer contributed to the crude HR by having the highest HR 8.84 (7.50–10.43), although after the first year of follow-up this decreased and at the 5-year follow-up timepoint, results were no longer statistically significant.

Cause-specific mortality

For cases the adjusted HR remained significant for all comorbidities; however, the highest HR was seen for cancer (1.45 (95%CI = 1.41–1.49) (*eTable 3*).

Table 2 outlines risk of all-cause mortality in patients with diverticular disease and their matched reference individuals. By the first-year follow-up, the HR (95% CI) was 1.83 (95%CI = 1.75–1.90), with HRs of around 1.2 thereafter. The increased risk of death among individuals with diverticular disease persisted up to and including 15 years postdiagnosis.

Also compared to siblings was there an increased morality (1.39; 95%CI 1.33–1.45), with the highest HRs seen (Table 3).

Individuals with diverticular disease whose colorectal histology had shown inflammation were at a + 36% increased risk of death (95%CI = 1.33–1.38) (*eTable 3*), with the highest HR seen in the first year of follow-up (HR = 2.18; 95%CI = 2.05–2.32). HRs for death were lower in diverticular disease patients with normal colorectal mucosa (HR = 1.21; 95%CI = 1.18–1.24) (P < .001 for interaction) but remained statistically significant also beyond 5 years after diverticular diagnosis (*eTable 4*).

Sensitivity analyses

Restricting the duration between diverticular disease ICD-code and SnoMed code to <1 year (HR = 1.30); excluding individuals with IBD (HR = 1.28), excluding any gastrointestinal surgery in the last 90 days (HR = 1.24), or restricting cases to those with diverticular disease as the primary diagnosis (HR = 1.21) did not change the risk estimates more than marginally (*eTable 5*).

Restricting data to the period since 2002, individuals with an ICD code in an inpatient setting had a higher mortality (HR = 1.66) than those first diagnosed in an outpatient setting (HR = 1.09).

Restricting follow-up to the first 3 years after diverticular disease diagnosis (to increase comparability), we found the lowest mortality in diverticular disease patients diagnosed in the last calendar period (2010–2017) (HR = 1.34; 95%CI = 1.29–1.40) (*eTable 6*).

Comparing inpatient to outpatients' diagnoses, patients requiring hospitalization at diagnosis of diverticular disease (HR = 1.66) had a higher mortality than outpatients at diagnosis (HR = 1.09) (*eTable 7*).

Discussion

In this nationwide study of more than 97,000 individuals with diverticular disease, we found overall that the risk of death was increased by 27%. In absolute terms, there was one extra death in 100 diverticular disease patients followed for 1 year compared to reference individuals (on average 4.4 vs. 3.4 deaths). This is consistent with earlier data from Sweden on diverticular disease inpatients [11]. In our study, the excess mortality was highest in the first year after diverticular disease diagnosis, remaining higher than the reference individuals for the remaining follow-up years. Of note, mortality risks were highest in diverticular disease patients with colorectal histology showing mucosal inflammation compared to normal morphology, however, most were not cancer related. Also of note, the mortality was lower in patients first diagnosed in an outpatient setting, suggesting that underlying comorbidity may play a role in these findings.

In this study inflammation linked with diverticular disease was noted as an excess morbidity risk. It must be noted that those with normal mucosa and diverticular disease also had an increased risk compared with reference individuals, although the risk was not as high.

Cause-specific death rates provided the opportunity to determine if specific comorbidity contributed significantly to mortality statistics. By stratifying and adjusting for all covariate parameters we were able to determine the mortality risk to diverticular disease patients from other death outcomes. Cancers (other and colorectal) greatly contributed to the mortality of patients. However, inflammation in the colonic mucosa further increased the HR signifying that although death may have occurred due to cancer (GI or other) or other non-GI causes, inflammation with diverticular

Table 1
Baseline characteristics of the study cohort

	Case n = 97,850	Reference individuals n = 453 634	Sibling n = 84 197
Gender			
Male, n (%)	40,428 (41)	185,587 (41)	42,060 (50)
Female, n (%)	57,422 (59)	268,047 (59)	42,137 (50)
Age			
Mean (SD)	63.9 (13.3)	63.5 (13.3)	56.1 (11.7)
Median (IQR)	65.0 (55.0–74.0)	65.0 (55.0–73.0)	57.0 (48.0–65.0)
Range, min-max	18.0–99.0	18.0–100.0	18.0–84.0
Categories, n (%)			
<30	1072 (1)	5140 (1)	1817 (2)
30–39	3617 (4)	17,554 (4)	5913 (7)
40–49	9735 (10)	46,945 (10)	15,468 (18)
50–59	19,047 (19)	90,780 (20)	25,350 (30)
60–69	28,229 (29)	131,952 (29)	25,339 (30)
70–79	24,903 (25)	112,891 (25)	9889 (12)
80+	11,247 (11)	48,372 (11)	421 (1)
Country of birth, n (%)			
Nordic	92,586 (95)	417,090 (92)	83,576 (99)
Other	5262 (5)	36,533 (8)	620 (1)
Missing	2 (0)	11 (0)	1 (0)
Level of education, n (%)			
Compulsory school, <= 9 y	33,087 (34)	154,792 (34)	24,743 (29)
Upper secondary school (10–12 y)	36,818 (38)	164,903 (36)	37,120 (44)
College or university (>= 13 y)	18,785 (19)	98,456 (22)	18,855 (22)
Missing	9160 (9)	35,483 (8)	3479 (4)
Start year of follow-up			
1987–1999	15,684 (16)	75,292 (17)	7471 (9)
2000–2009	38,490 (39)	178,885 (39)	30,892 (37)
2010–2017	43,676 (45)	199,457 (44)	45,834 (54)
Time in years between first diagnosis and biopsy			
Mean (SD)	4.0 (6.0)		
Median (IQR)	0.7 (0.0–6.1)		
Range, min-max	0.0–42.4		
N in/out visits/admissions for 365 d prior, n (%)			
0	34,271 (35)	292,201 (64)	50,996 (61)
1	20,362 (21)	63,961 (14)	12,598 (15)
2	12,384 (13)	32,549 (7)	6662 (8)
3+	30,833 (32)	64,923 (14)	13,941 (17)
Prior inflammatory bowel disease, n (%)	2195 (2.2)	410 (0.1)	327 (0.4)
Prior cardiovascular disease, n (%)	8617 (8.8)	24,986 (5.5)	3305 (3.9)
Prior ischemic heart disease, n (%)	3653 (3.7)	10,954 (2.4)	1667 (2.0)
Prior thromboembolic disease, n (%)	1724 (1.8)	3466 (0.8)	512 (0.6)
Prior deep venous thrombosis, n (%)	749 (0.8)	1523 (0.3)	202 (0.2)
Prior cerebrovascular disease, n (%)	2340 (2.4)	8760 (1.9)	972 (1.2)
Prior congestive heart failure, n (%)	2070 (2.1)	5181 (1.1)	471 (0.6)
Prior cancer, n (%)	7912 (8.1)	18,722 (4.1)	3503 (4.2)
Prior respiratory disease, n (%)	10,182 (10.4)	24,980 (5.5)	5267 (6.3)
Diabetes, n (%)	1920 (2.0)	5985 (1.3)	999 (1.2)
Chronic obstructive pulmonary disease (COPD), n (%)	1258 (1.3)	2409 (0.5)	417 (0.5)
Obesity/Dyslipidemia, n (%)	3483 (3.6)	8829 (1.9)	1874 (2.2)
Alcohol related disease, n (%)	754 (0.8)	2101 (0.5)	527 (0.6)

Baseline comorbidities are defined as any hospital contact within 5 years prior to index.

disease likely further adds to a patients overall comorbid risk of mortality.

In comparison to our findings, another population-based study defining the HR for long (up to 15 years) and short term (up to 5 years) [26] found similar results for hospital inpatients in Sweden, albeit with a higher initial risk estimate. In the first 6 months after admission for diverticular disease, the odds ratios for colorectal cancer were up to 31.49 (95% CI 19.00–52.21) compared to the current study, where the HR *for death* from colorectal cancer was 8.76 (7.43–10.33). After the first year, there was no further association between diverticular disease and colorectal cancer death. The number of colon cancer deaths only represented a small number of total deaths in the overall diverticular disease group.

Inflammation in all-cause mortality has been previously assessed by examining the prognostic relationship between C-reactive protein (CRP) and albumin (modified Glasgow Prognostic Score), to assess systemic inflammation [27]. Systemic inflammatory markers and non-GI mortality have further been explored in a recent review which demonstrated that elevated serum C-reactive protein (CRP) levels in patients with type 2 diabetes were associated with comorbid systemic inflammation from future cardiovascular and all-cause mortality [28]. Systemic inflammation (using inflammatory markers, CRP levels, and neutrophil count) was also linked in another study where these markers of inflammation were predictive of increased mortality due to all-cause, cancer, and cardiovascular disease [27].

A recent study showed an association between fecal immunochemical blood (FIT) results and mortality in a South Korean population [29]. FIT directly measures human f-HB (fecal hemoglobin) in fecal samples for colorectal cancer screening, but aside from colorectal cancer mortality outcomes this study also showed that FIT levels were also high in patients with systemic inflammation from other non-GI comorbidities. This association may reflect increased subclinical colonic inflammation, which we report to be associated with further increasing the risk of mortality [29]. Studies that have reported f-HB as a useful gut inflammatory marker have been un-

Table 2
Cox models – subgroups. Risk of all-cause mortality in patients with diverticular disease (Case) and matched general population reference individuals (Reference)

	N% case	N% reference	PY case	PY reference	Evs case	Evs reference	IR case	IR reference	HR (95% CI) Case*	HR (95% CI) Reference**
Overall	97,850 (100.0%)	453,634 (100.0%)	749,545	374,3241	32,959 (33.7%)	127,153 (28.0%)	44.0 (43.5–44.4)	34.0 (33.8–34.2)	1.34 (1.32–1.36)	1.27 (1.25–1.29)
Follow-up										
<1 y	97,850 (100.0%)	453,634 (100.0%)	94,106	447,314	5733 (5.9%)	11,290 (2.5%)	60.9 (59.4–62.5)	25.2 (24.8–25.7)	2.35 (2.27–2.43)	1.83 (1.75–1.90)
1–5 y	91,943 (94.0%)	440,633 (97.1%)	303,110	1 475,053	10,870 (11.8%)	42,207 (9.6%)	35.9 (35.2–36.5)	28.6 (28.3–28.9)	1.22 (1.19–1.25)	1.17 (1.15–1.20)
>5 y	58,926 (60.2%)	291,690 (64.3%)	352,328	18,20,874	16,356 (27.8%)	73,656 (25.3%)	46.4 (45.7–47.1)	40.5 (40.2–40.7)	1.21 (1.19–1.23)	1.19 (1.17–1.22)
Sex										
Women	57,422 (58.7%)	268,047 (59.1%)	448,230	22,42,688	19,107 (33.3%)	75,207 (28.1%)	42.6 (42.0–43.2)	33.5 (33.3–33.8)	1.32 (1.30–1.35)	1.26 (1.24–1.28)
Men	40,428 (41.3%)	185,587 (40.9%)	301,315	15,00,553	13,852 (34.3%)	51,946 (28.0%)	46.0 (45.2–46.7)	34.6 (34.3–34.9)	1.37 (1.34–1.40)	1.28 (1.26–1.31)
Age										
<30 y	1072 (1.1%)	5140 (1.1%)	9257	44,911	27 (2.5%)	42 (0.8%)	2.9 (1.9–4.2)	0.9 (0.7–1.3)	3.06 (1.88–4.98)	2.55 (1.49–4.37)
30 y–39 y	3617 (3.7%)	17,554 (3.9%)	34,200	168,186	159 (4.4%)	441 (2.5%)	4.6 (4.0–5.4)	2.6 (2.4–2.9)	1.78 (1.48–2.15)	1.71 (1.41–2.07)
40 y–49 y	9735 (9.9%)	46,945 (10.3%)	95,532	472,374	829 (8.5%)	2583 (5.5%)	8.7 (8.1–9.3)	5.5 (5.3–5.7)	1.57 (1.45–1.71)	1.50 (1.38–1.63)
50 y–59 y	19,047 (19.5%)	90,780 (20.0%)	175,668	874,156	2964 (15.6%)	10,271 (11.3%)	16.9 (16.3–17.5)	11.7 (11.5–12.0)	1.44 (1.38–1.50)	1.37 (1.31–1.43)
60 y–69 y	28,229 (28.8%)	131,952 (29.1%)	221,456	11,09,469	7934 (28.1%)	28,953 (21.9%)	35.8 (35.0–36.6)	26.1 (25.8–26.4)	1.41 (1.37–1.45)	1.35 (1.31–1.39)
70 y–79 y	24,903 (25.5%)	112,891 (24.9%)	163,055	827,826	12,884 (51.7%)	50,798 (45.0%)	79.0 (77.7–80.4)	61.4 (60.8–61.9)	1.34 (1.31–1.37)	1.26 (1.23–1.29)
80+	11,247 (11.5%)	48,372 (10.7%)	50,376	246,319	8162 (72.6%)	34,065 (70.4%)	162.0 (158.5–165.6)	138.3 (136.8–139.8)	1.22 (1.18–1.25)	1.13 (1.10–1.16)
Year										
1987–1999	15,684 (16.0%)	75,292 (16.6%)	208,314	11,09,122	10,896 (69.5%)	47,119 (62.6%)	52.3 (51.3–53.3)	42.5 (42.1–42.9)	1.31 (1.29–1.34)	1.26 (1.23–1.28)
2000–2009	38,490 (39.3%)	178,885 (39.4%)	359,492	17,76,839	15,694 (40.8%)	59,425 (33.2%)	43.7 (43.0–44.3)	33.4 (33.2–33.7)	1.32 (1.30–1.34)	1.27 (1.24–1.29)
2010–2017	43,676 (44.6%)	199,457 (44.0%)	181,738	857,279	6369 (14.6%)	20,609 (10.3%)	35.0 (34.2–35.9)	24.0 (23.7–24.4)	1.42 (1.38–1.47)	1.38 (1.34–1.42)
Country of birth										
Nordic	92,586 (94.6%)	417,090 (91.9%)	711,540	34,65,051	31,710 (34.2%)	120,916 (29.0%)	44.6 (44.1–45.1)	34.9 (34.7–35.1)	1.34 (1.32–1.36)	1.24 (1.22–1.26)
Other	5262 (5.4%)	36,533 (8.1%)	37,981	278,130	1249 (23.7%)	6237 (17.1%)	32.9 (31.1–34.8)	22.4 (21.9–23.0)	1.35 (1.14–1.59)	1.33 (1.12–1.58)
Level of education										
Compulsory school, <= 9 y	33,087 (33.8%)	154,792 (34.1%)	259,997	12,93,627	14,321 (43.3%)	61,528 (39.7%)	55.1 (54.2–56.0)	47.6 (47.2–47.9)	1.21 (1.19–1.23)	1.16 (1.14–1.18)
Upper secondary school (10–12 y)	36,818 (37.6%)	164,903 (36.4%)	286,048	13,35,071	8816 (23.9%)	32,479 (19.7%)	30.8 (30.2–31.5)	24.3 (24.1–24.6)	1.30 (1.27–1.33)	1.26 (1.23–1.29)
College or university (>= 13 y)	18,785 (19.2%)	98,456 (21.7%)	141,294	786,532	3156 (16.8%)	12,042 (12.2%)	22.3 (21.6–23.1)	15.3 (15.0–15.6)	1.40 (1.35–1.46)	1.37 (1.31–1.42)
Missing	9,160 (9.4%)	35,483 (7.8%)	62,206	328,010	6666 (72.8%)	21,104 (59.5%)	107.2 (104.6–109.8)	64.3 (63.5–65.2)	1.71 (1.66–1.76)	1.56 (1.51–1.60)
Diverticular disease										
Diagnosis before histology	63,069 (64.5%)	302,808 (66.8%)	513,728	26,34,435	22,456 (35.6%)	91,335 (30.2%)	43.7 (43.1–44.3)	34.7 (34.4–34.9)	1.30 (1.28–1.32)	1.25 (1.23–1.27)
Histology before diagnosis	34,365 (35.1%)	148,499 (32.7%)	231,209	10,83,026	10,485 (30.5%)	35,618 (24.0%)	45.3 (44.5–46.2)	32.9 (32.5–33.2)	1.38 (1.35–1.41)	1.32 (1.29–1.35)
Comorbidity										
CVD	8617 (8.8%)	24,986 (5.5%)	39,768	125,391	4,664 (54.1%)	12,229 (48.9%)	117.3 (113.9–120.7)	97.5 (95.8–99.3)	1.28 (1.23–1.32)	1.26 (1.22–1.31)
Cancer	7912 (8.1%)	18,722 (4.1%)	40,950	102,683	2,894 (36.6%)	5247 (28.0%)	70.7 (68.1–73.3)	51.1 (49.7–52.5)	1.34 (1.28–1.41)	1.24 (1.19–1.30)
Respiratory	10,182 (10.4%)	24,980 (5.5%)	49,381	130,297	3613 (35.5%)	8035 (32.2%)	73.2 (70.8–75.6)	61.7 (60.3–63.0)	1.27 (1.22–1.32)	1.27 (1.22–1.32)
IBD	2195 (2.2%)	410 (0.1%)	14,016	2334	615 (28.0%)	104 (25.4%)	43.9 (40.5–47.5)	44.6 (36.4–54.0)	1.04 (0.84–1.28)	1.14 (0.92–1.40)

* Stratified Cox.
** Stratified Cox + adjustment for education level and comorbidities: CVD, Cancer, Respiratory disease, and inflammatory bowel disease.Evs=Events.

Table 3
Cox models – subgroup versus siblings. Risk of all-cause mortality in patients with diverticular disease (Case) and siblings (Siblings)

	N% Case	N% Siblings	PY case	PY siblings	Evs case	Evs siblings	IR case	IR siblings	HR (95% CI) case*	HR (95% CI) siblings†
Overall	41,843 (100.0%)	84 197 (100.0%)	328 454	689 488	5647 (13.5%)	7784 (9.2%)	17.2 (16.7–17.6)	11.3 (11.0–11.5)	1.46 (1.40–1.52)	1.39 (1.33–1.45)
Follow-up										
<1 y	41,843 (100.0%)	84 197 (100.0%)	41 221	83,662	986 (2.4%)	820 (1.0%)	23.9 (22.5–25.5)	9.8 (9.1–10.5)	2.28 (2.06–2.52)	1.68 (1.47–1.93)
1–5 y	40,781 (97.5%)	83,008 (98.6%)	134 740	277 412	2005 (4.9%)	2788 (3.4%)	14.9 (14.2–15.5)	10.1 (9.7–10.4)	1.42 (1.33–1.51)	1.41 (1.32–1.51)
>5 y	26,011 (62.2%)	54,302 (64.5%)	152 493	328 414	2656 (10.2%)	4176 (7.7%)	17.4 (16.8–18.1)	12.7 (12.3–13.1)	1.29 (1.22–1.37)	1.30 (1.23–1.38)
Sex										
Women	23,239 (55.5%)	42,137 (50.0%)	182 771	346 868	2777 (11.9%)	3246 (7.7%)	15.2 (14.6–15.8)	9.4 (9.0–9.7)	1.44 (1.34–1.55)	1.35 (1.26–1.46)
Men	18,604 (44.5%)	42,060 (50.0%)	145 683	342 621	2870 (15.4%)	4538 (10.8%)	19.7 (19.0–20.4)	13.2 (12.9–13.6)	1.46 (1.36–1.57)	1.42 (1.31–1.53)
Age										
<30 y	753 (1.8%)	1817 (2.2%)	6338	17 255	21 (2.8%)	24 (1.3%)	3.3 (2.1–5.1)	1.4 (0.9–2.1)	2.94 (1.19–7.26)	3.90 (1.27–11.98)
30 y–39 y	2577 (6.2%)	5913 (7.0%)	24 817	60,806	109 (4.2%)	153 (2.6%)	4.4 (3.6–5.3)	2.5 (2.1–2.9)	1.80 (1.24–2.60)	1.81 (1.23–2.66)
40 y–49 y	6702 (16.0%)	15,468 (18.4%)	66 043	157 688	509 (7.6%)	840 (5.4%)	7.7 (7.1–8.4)	5.3 (5.0–5.7)	1.47 (1.25–1.73)	1.45 (1.22–1.72)
50 y–59 y	11,935 (28.5%)	25,350 (30.1%)	107 954	227 706	1454 (12.2%)	2287 (9.0%)	13.5 (12.8–14.2)	10.0 (9.6–10.5)	1.28 (1.16–1.40)	1.24 (1.13–1.37)
60 y–69 y	13,928 (33.3%)	25,339 (30.1%)	95 428	176 130	2296 (16.5%)	2960 (11.7%)	24.1 (23.1–25.1)	16.8 (16.2–17.4)	1.46 (1.35–1.57)	1.35 (1.24–1.46)
70 y–79 y	5703 (13.6%)	9889 (11.7%)	27 255	48,788	1208 (21.2%)	1463 (14.8%)	44.3 (41.9–46.9)	30.0 (28.5–31.6)	1.61 (1.43–1.81)	1.54 (1.35–1.75)
80+	245 (0.6%)	421 (0.5%)	619	1115	50 (20.4%)	57 (13.5%)	80.7 (59.9–106.5)	51.1 (38.7–66.2)	3.79 (1.16–12.38)	Not calculated. ‡
Year										
1987–1999	3365 (8.0%)	7471 (8.9%)	65 687	148 054	915 (27.2%)	1434 (19.2%)	13.9 (13.0–14.9)	9.7 (9.2–10.2)	1.31 (1.21–1.42)	1.29 (1.19–1.40)
2000–2009	15,134 (36.2%)	30,892 (36.7%)	163 049	341 639	2762 (18.3%)	3843 (12.4%)	16.9 (16.3–17.6)	11.2 (10.9–11.6)	1.44 (1.37–1.52)	1.44 (1.37–1.51)
2010–2017	23,344 (55.8%)	45,834 (54.4%)	99 717	199 795	1970 (8.4%)	2507 (5.5%)	19.8 (18.9–20.6)	12.5 (12.1–13.0)	1.52 (1.44–1.62)	1.51 (1.43–1.61)
Country of birth										
Nordic	41,524 (99.2%)	83,576 (99.3%)	326 174	684 942	5610 (13.5%)	7748 (9.3%)	17.2 (16.8–17.7)	11.3 (11.1–11.6)	1.46 (1.40–1.52)	1.39 (1.33–1.45)
Other	319 (0.8%)	620 (0.7%)	2 279	4 543	37 (11.6%)	36 (5.8%)	16.2 (11.4–22.4)	7.9 (5.6–11.0)	1.93 (1.05–3.53)	1.28 (0.63–2.59)
Level of education										
Compulsory school, <= 9 y	11,339 (27.1%)	24,743 (29.4%)	91 112	206 299	2071 (18.3%)	3322 (13.4%)	22.7 (21.8–23.7)	16.1 (15.6–16.7)	1.35 (1.28–1.43)	1.33 (1.26–1.41)
Upper secondary school (10–12 y)	18,601 (44.5%)	37 120 (44.1%)	145 091	297 680	2092 (11.2%)	2 817 (7.6%)	14.4 (13.8–15.0)	9.5 (9.1–9.8)	1.43 (1.35–1.52)	1.40 (1.33–1.49)
College or university (>= 13 y)	10,066 (24.1%)	18,855 (22.4%)	76 198	147 540	792 (7.9%)	961 (5.1%)	10.4 (9.7–11.1)	6.5 (6.1–6.9)	1.48 (1.35–1.63)	1.47 (1.33–1.61)
Missing	1,837 (4.4%)	3479 (4.1%)	16 053	37,970	692 (37.7%)	684 (19.7%)	43.1 (40.0–46.4)	18.0 (16.7–19.4)	2.01 (1.81–2.24)	1.77 (1.59–1.98)
Diverticular disease										
Diagnosis before histology	26,648 (63.7%)	54,002 (64.1%)	223 965	473 572	3795 (14.2%)	5204 (9.6%)	16.9 (16.4–17.5)	11.0 (10.7–11.3)	1.46 (1.40–1.52)	1.45 (1.39–1.51)
Histology before diagnosis	14,572 (34.8%)	28,955 (34.4%)	100 165	206 210	1774 (12.2%)	2503 (8.6%)	17.7 (16.9–18.6)	12.1 (11.7–12.6)	1.38 (1.30–1.46)	1.36 (1.28–1.45)
Comorbidity										
CVD	2425 (5.8%)	3305 (3.9%)	12 294	18,064	618 (25.5%)	546 (16.5%)	50.3 (46.4–54.4)	30.2 (27.7–32.9)	1.66 (1.48–1.86)	1.68 (1.50–1.89)
Cancer	2985 (7.1%)	3503 (4.2%)	16 011	19,013	459 (15.4%)	312 (8.9%)	28.7 (26.1–31.4)	16.4 (14.6–18.3)	1.70 (1.47–1.96)	1.51 (1.31–1.75)
Respiratory	4188 (10.0%)	5267 (6.3%)	22 556	29,885	672 (16.0%)	609 (11.6%)	29.8 (27.6–32.1)	20.4 (18.8–22.1)	1.46 (1.30–1.63)	1.45 (1.30–1.62)
IBD	1032 (2.5%)	327 (0.4%)	6 961	1779	104 (10.1%)	32 (9.8%)	14.9 (12.2–18.1)	18.0 (12.3–25.4)	0.92 (0.62–1.38)	0.91 (0.61–1.37)

* Stratified Cox + adjustment for age and gender.
† Stratified Cox + adjustment for age, gender, education level, and comorbidities: CVD, Cancer, Respiratory disease, and Inflammatory bowel disease.
‡ Not calculated due to lack of events.

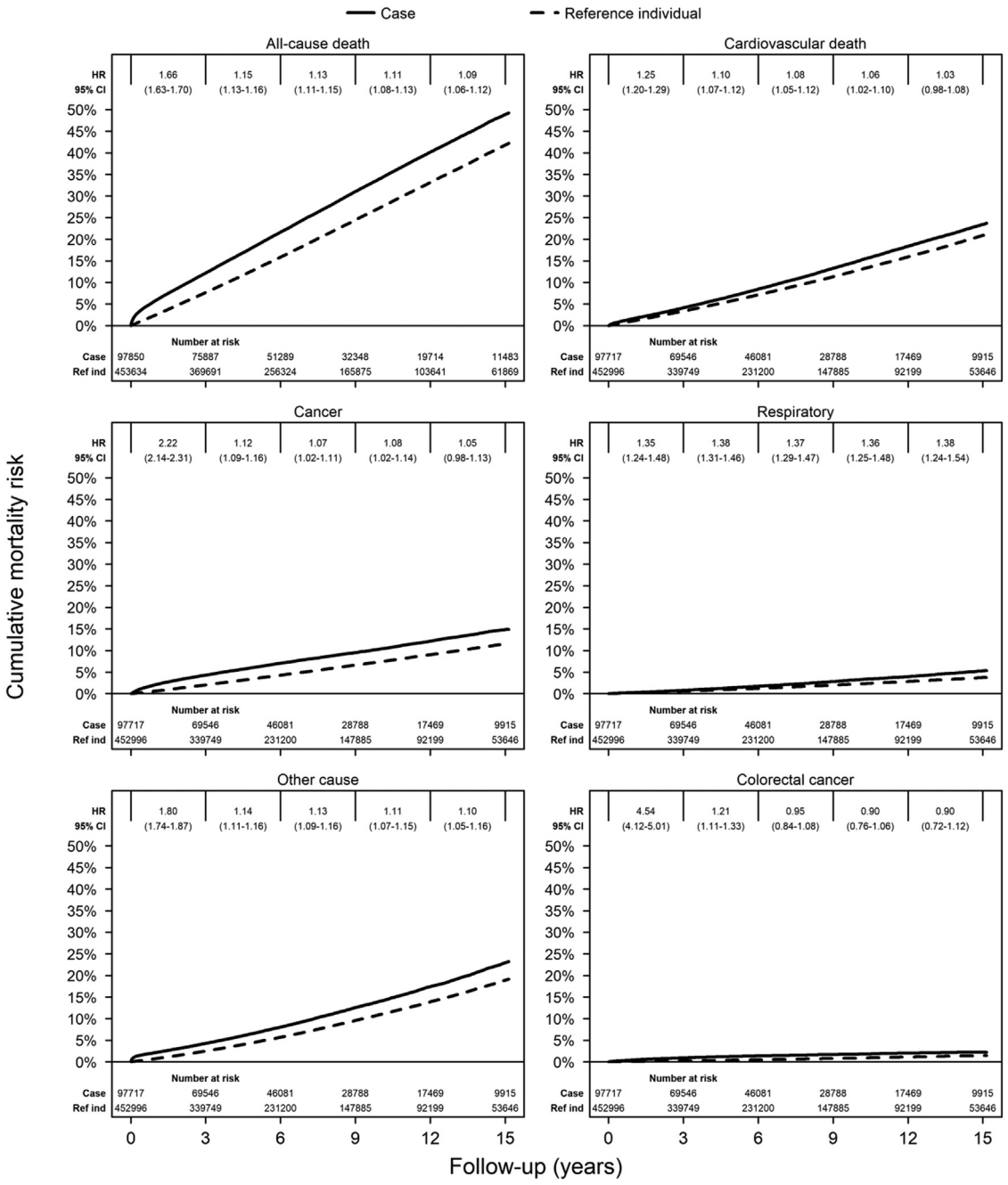

Fig. 2. Kaplan-Meier plots. Long term (up to 15 years). Cumulative Incidence over follow-up years for cases and reference individuals, with HR (95% CI) and numbers at risk: All-cause death, Cardiovascular death, Cancer, Respiratory, Other cause, and Colorectal cancer. Kaplan-Meier curves – Curves and Hazard ratios are unadjusted.

dertaken in ulcerative colitis patients in recent remission [30], as well as being used as a screening tool for IBD patients [31], with results to support the use of f-HB testing as a prognostic tool of gut inflammation, with a prelude to addressing colonic disease progression and the decrease of mortality risk [30].

The study had several strengths. We used two reference groups, matched reference individuals from the general population, and siblings. The large number of diverticular disease patients allowed for stratifying and adjusting for demographics and comorbidities. The large cohort numbers provided information on over 32,000 deaths in diverticular disease patients over the timeline. There was also a long follow-up time of over 15 years with negligible loss, and we were able to calculate mortality estimates greater than 10 years after diagnosis. In Sweden, all residents have a personal identification number allowing linkages to government and health registers and follow-up of emigration. Through the personal identity numbers, study participants can be tracked for their lifetime with virtually no loss of follow-up. There are few studies with the availability of this quantity and quality of data.

Comparisons with siblings reduced the influence of shared early environmental risks and shared genetics. The results showed that indeed, patients with diverticular disease did have a 68% increased risk of all-cause mortality compared to their siblings. This provided clarification that early shared environmental risk factors and shared genetics are very unlikely to cofound the data.

Utilizing the Swedish Patient Register for acquiring ICD codes for diverticular disease, a likely high specificity (PPV) of 85%–95% is expected [21]. A Danish study (with a similar healthcare system

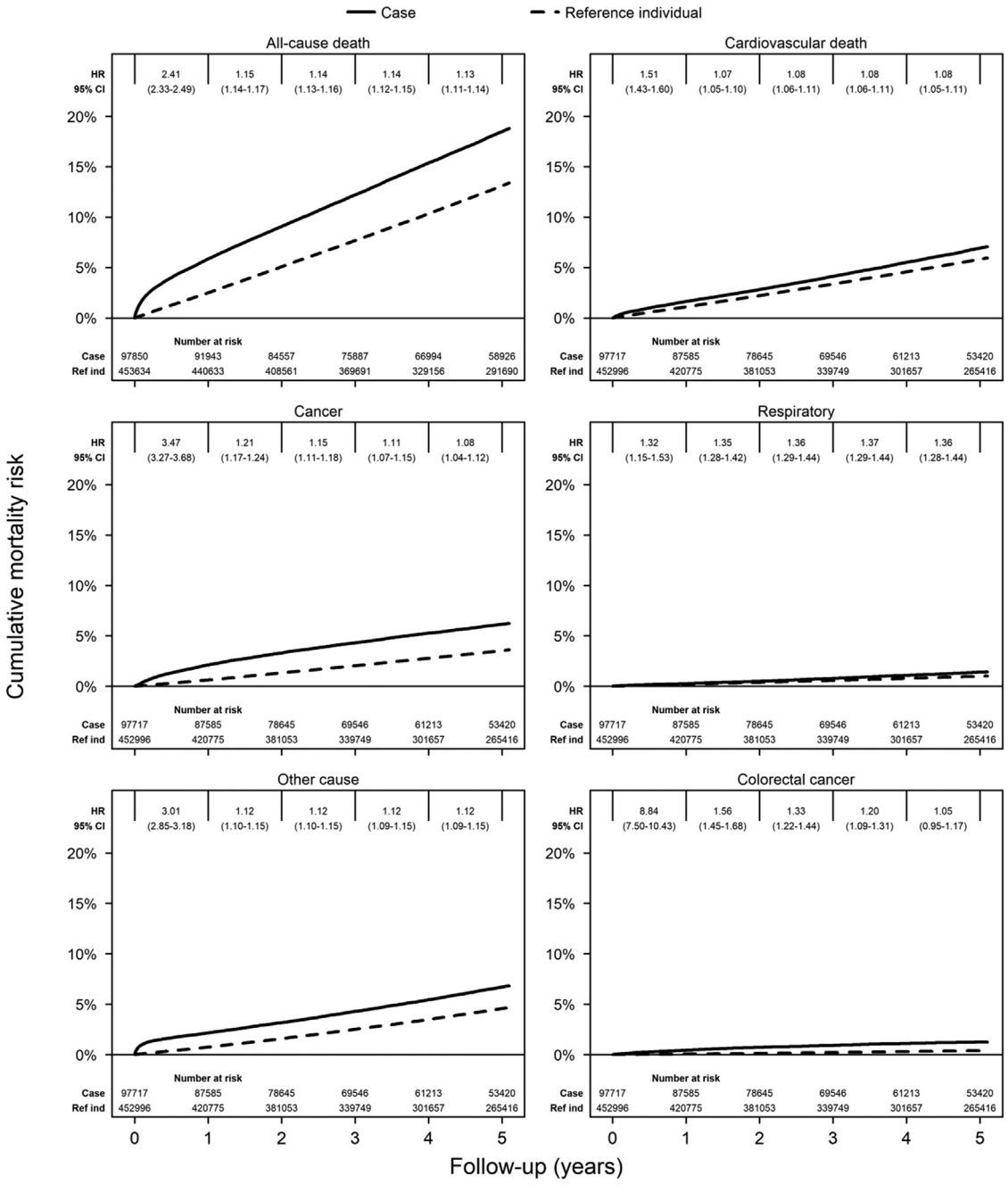

Fig. 3. Kaplan-Meier plots. Short term (up to 5 years). Cumulative Incidence over follow-up years for cases and reference individuals, with HR (95% CI) and numbers at risk: All-cause death, Cardiovascular death, Cancer, Respiratory, Other cause, and Colorectal cancer. Kaplan-Meier curves – Curves and Hazard ratios are unadjusted.

as in Sweden) [32], found a positive predictive value of 98% for the K57 ICD code we used in the current study [33].

By identifying case characteristics pertaining to histology results from the 28 Swedish pathology departments, the specificity would be pushed even higher, further giving validity to the study results. To further adjust for multiple confounders, country of birth (representing ethnicity which is not recorded in Swedish registers), as well as education level (as a proxy for socioeconomic status) was used for statistical adjustment and stratification. This allowed for analyses to be conducted within the subgroups to investigate heterogeneous results, and to determine if one subgroup had a higher risk of cause-specific mortality risk.

The study also had limitations in its approach to defining the cohort of diverticular disease patients in terms of their pathology. Study inclusion was conditional on having both a relevant ICD code and colorectal histopathology. While this may have limited the study size, substantial selection bias is unlikely. Recent guidelines recommend a follow-up colonoscopy after the first episode of acute diverticulitis to rule out colorectal cancer [34,26]. Compared to another Swedish study [11], our annual incidence of diverticular disease with histopathology was still about 80% of that of the Granlund et al. study (not requiring histopathology) arguing against substantial selection bias. Still, we cannot rule out the presence of misclassification and that our data collation may have biased the study results, most likely towards the null [34]. Of note, our follow-up continued up until 2017, compared with 2010 in the earlier Swedish study [3].

Further limitations to this study were the inability to define colonic inflammation in terms of severity, as well as the location in the mucosal tissue. So, while inflammation in the first year in-

creased mortality in patients with known diverticulae, we cannot know for certain if the biopsies were obtained within the region of the diverticulum or elsewhere in the colon. Thus, an increase in inflammation in these patients cannot be pinpointed to inflammation in the diverticulae contained colon but may be attributed to generic colonic histological inflammation in a colon that also contains diverticulae. Biopsies only capture the mucosal tissue, and occasionally the submucosa. They do not capture deep enough into the deeper layers of the colon for ascertaining the true level of inflammation in a diverticulum section of the colon [35].

Our study was not able to distinguish between symptomatic uncomplicated diverticular disease (SUDD), acute uncomplicated, or acute complicated diverticulitis due to the nature of the dataset information available. Further studies would benefit by having the ability to classify patients with diverticulosis, and diverticular disease. This would ideally be achieved by obtaining data specific to inflammation histopathology reports of diverticulum-contained colon resection samples and repeating this analysis to record inflammation in all layers of the colon section pertaining to the penetration depth and surrounding tissue of the diverticulum. The rationale is being that patients who do present with episodes of uncomplicated acute diverticulitis may continue to have a prolonged inflammation present long after successful treatment [36]; often referred to as post-AD SUDD [37]. The rate of reinfection in acute uncomplicated diverticulitis patients was assessed in 2013 [38], and it was determined that inflammation does continue in a subset of patients postsuccessful treatment of their attack, identifying endoscopic and histological inflammation as a significant predictor of recurrence.

Further to this, it was also beyond the scope of this study to examine, and adjust for, the impact of medications, smoking, diet, or physical activity, on mortality in diverticular disease.

Conclusion

This study investigated cause-specific mortality in individuals diagnosed with diverticular disease in Sweden between 1987 and 2017. Results revealed that patients with diverticular disease and mucosal inflammation at histopathology had a higher mortality than diverticula disease patients with normal mucosa, within the first-year postdiagnosis. This appears to contribute to overall diverticular disease mortality rates, and as such further research is needed to better understand the role of mucosal colonic inflammation in diverticula disease.

Contributors

RC wrote the first draft of the paper. RC, JFL, MW, and NT conceived and designed the study with input from the other authors. JFL and MW supervised the project. JFL funded the study. MT carried out the statistics. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version.

JFL takes responsibility for the integrity of the data and the accuracy of the data analyses. JFL is the guarantor of the data.

Disclaimer

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Details of ethics approval

This project (2014/1287–31/4) was approved by the Research Ethics Committee in Stockholm, Sweden on August 27, 2014.

Transparency

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2022.10.006.

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