BMJ Open

Type 2 diabetes and risk of diverticular disease: a Danish cohort study

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To cite: Wittström F, Skajaa N, Bonnesen K, *et al*. Type 2 diabetes and risk of diverticular disease: a Danish cohort study. *BMJ Open* 2022;**12**:e059852. doi:10.1136/bmjopen-2021-059852

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059852).

Received 03 December 2021
Accepted 02 February 2022

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ABSTRACT

Objectives To investigate the association between type 2 diabetes and risk of diverticular disease. Unlike previous studies, which have found conflicting results, we aimed to distinguish between diabetes types and adjust for modifiable risk factors.

Design Observational cohort study.

Setting Population-based Danish medical databases, covering the period 2005–2018.

Participants Respondents of the 2010 or the 2013 Danish National Health Survey, of which there were 15 047 patients with type 2 diabetes and 210 606 patients without diabetes.

Primary and secondary outcome measures Hazard ratios (HRs) for incident hospital diagnosis of diverticular disease adjusted for survey year, sex, age, body mass index (BMI), physical activity intensity, smoking behaviour, diet and education based on Cox regression analysis. As latency may affect the association between type 2 diabetes and diverticular disease, patients with type 2 diabetes were stratified into those with <2.5, 2.5–4.9 and ≥5 years duration of diabetes prior to cohort entry.

Results For patients with and without diabetes the incidence rates of diverticular disease were 0.76 and 0.54 events per 1000 person years, corresponding to a crude HR of 1.08 (95% CI 1.00 to 1.16) and an adjusted HR of 0.88 (95% CI 0.80 to 0.96). The HR was lower among patients with ≥5 years duration of diabetes (adjusted HR: 0.76, 95% CI 0.67 to 0.87) than among those with 2.5–4.9 years or <2.5 years duration.

Conclusion We found that patients with type 2 diabetes had a higher incidence rate of diverticular disease compared with patients without diabetes. However, after adjustment for modifiable risk factors, driven by BMI, type 2 diabetes appeared to be associated with a slightly lower risk of diverticular disease. Lack of adjustment for BMI may partially explain the conflicting findings of previous studies.

Strengths and limitations of this study

- ► This is a nationwide prospective cohort study of Danish adults investigating the association between type 2 diabetes and diverticular disease.
- ► No previous study has investigated type 2 diabetes specifically and included adjustment for modifiable risk factors, most notably body mass index.
- ► We use registry data with high-positive predictive values to define both exposure and outcome in a setting of a free tax-supported healthcare system.
- ► Our data on modifiable risk factors are susceptible to bias from missing values, which we have attempted to address through a complete case analysis.
- ► Our outcome of a discharge diagnosis of diverticular disease is sensitive to diagnostic surveillance as diverticulosis is often asymptomatic, which we have attempted to address through stratification on colonoscopy status and analysis of diverticular disease complications.

INTRODUCTION

Diverticular disease occurs by herniation of mucosa and submucosa through the muscle layer of the colonic wall.[1] The condition affects more than 50% of individuals older than 60 years of age, but remains asymptomatic in most cases.[2] Around 5% develop diverticulitis, which can lead to complications such as abscess or perforation that may require surgical intervention.[2]

The pathophysiology of diverticular disease remains poorly understood.[1] However, several risk factors have consistently been associated with diverticular disease, including obesity, physical inactivity, smoking and low dietary fibre intake.[2] Current theories propose that chronic inflammation and gut microbial dysbiosis, both associated with these modifiable risk factors, play important roles in the pathogenesis.[1 2]

Diabetes mellitus has more than doubled in prevalence globally over the past three decades.[3] Type 2 diabetes is the most common form, and the rapid increase in global diabetes prevalence may be the result of lifestyle changes contributing to type 2 diabetes development.[3 4]

Diabetes exhibits an ambiguous association with diverticular disease. A meta-analysis of six studies examining the risk of diverticular disease after diabetes estimated a pooled odds ratio (OR) of 1.25 (95% confidence interval (CI) 0.87 to 1.79), but the findings from the individual studies were divergent.[5] As such, studies included in the meta-analysis and more recent studies have suggested that

diabetes increased,[6–8] decreased[9 10] or had no impact[11–14] on the risk of diverticular disease. In addition, most studies did not discern diabetes type (eg, type 1 or 2) and had limited data on potential confounding factors.

The mechanisms explaining this putative association are not clear. Obesity or low intake of dietary fibre in association with diabetes, as well as a genetic liability to type 2 diabetes, have been proposed to contribute to an increased risk,[5 6 15] while gradual lifestyle changes as part of diabetes treatment as well as associated drug therapy may contribute to a decreased risk.[10]

We conducted a nationwide prospective cohort study of Danish adults distinguishing between diabetes types and controlling for confounding from modifiable risk factors to investigate the association between type 2 diabetes and the subsequent risk of diverticular disease.

METHODS

Setting, design and data sources

We conducted a cohort study among first-time respondents of the 2010 or the 2013 Danish National Health Survey (DNHS),[16] followed until 31 December 2018. The DNHS is a recurring population-based survey comprising a representative sample of the adult Danish population. The survey design is described in detail elsewhere.[16] Data collection was finished in early May for both surveys; thus, 1 May was defined as the 'index date'. The self-administrated questionnaire was fully or partially completed by 177 639 (60%) respondents in 2010 and 162 283 (54%) respondents in 2013.

Using the Danish Civil Personal Registration number,[17] assigned to each resident at birth or on immigration, we linked the cohort to the Danish National Patient Registry (DNPR)[18] and the Danish National Health Service Prescription Database (DNHSPD).[19] The DNPR includes data on all inpatient non-psychiatric diagnoses since 1977 and on all outpatient clinic and emergency department diagnoses since 1995, coded according to the *International Classification of Diseases* (ICD). We searched for primary (main reason for hospital contact) or secondary (other relevant diseases related to the current hospital contact), inpatient or outpatient discharge diagnoses in the DNPR. The DNPR also holds data on surgical procedures since 1996, coded according to the *Nordic Medico-Statistical Committee System* (NOMESCO). The DNHSPD contains data on all reimbursed prescriptions redeemed at community pharmacies and hospital-based outpatient pharmacies since 2004, coded according to the *Anatomical Therapeutic Chemical Classification System* (ATC). For this study, data from these registries covered the period 2005–2018.

Patients with and without type 2 diabetes

We assembled a cohort of patients with type 2 diabetes by identifying patients that before the index date had a hospital-based diagnosis of diabetes or a redeemed prescription for glucose-lowering medication at or above 40 years of age.[20] This age was chosen to include most patients with type 2 diabetes while also excluding most patients with type 1 diabetes, gestational diabetes and polycystic ovary syndrome.[20] The positive predictive values of diagnostic and glucose-lowering medication coding for diabetes in Danish registries, measured against a gold standard of a diagnosis of diabetes confirmed by the patients' general practitioner, are estimated to be 97% and 95%, respectively.[21]

We excluded patients with a history of diverticular disease, inflammatory bowel disease and colorectal cancer before the index date, the last two due to the colonoscopic surveillance associated with these conditions. Patients without diabetes acted as comparators and were those aged 40 years or above not meeting the type 2 diabetes cohort eligibility criteria and not fulfilling the exclusion criteria. A study flow chart is provided in figure 1.

As type 2 diabetes gradually contributes to physiological changes,[4] latency may affect the association between type 2 diabetes and diverticular disease. We therefore

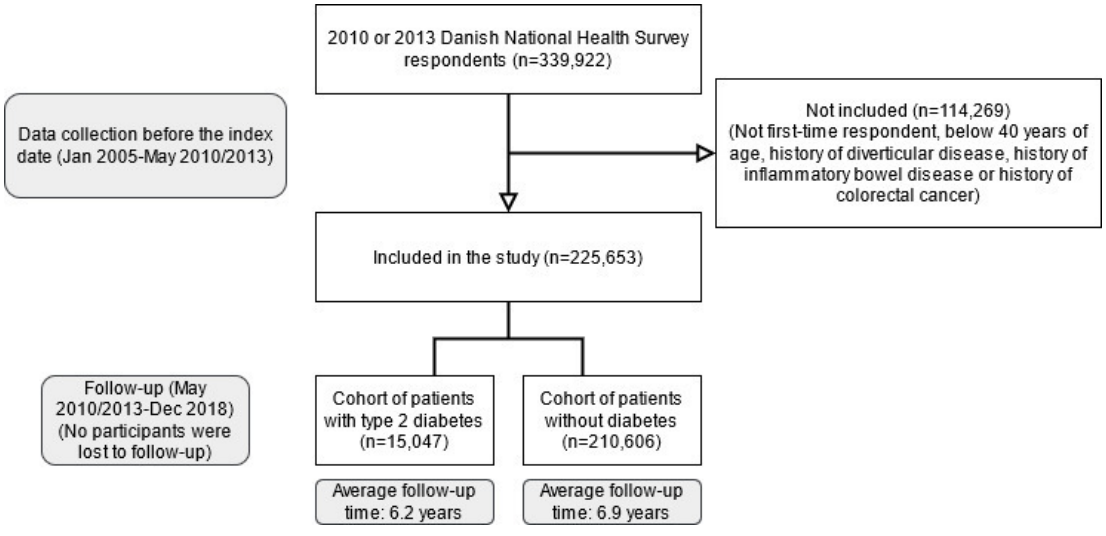

Figure 1 Study flow chart.

stratified patients with type 2 diabetes into those with shorter (<2.5 years), moderate (2.5–4.9 years) and longer (≥5 years) duration of diabetes prior to cohort entry. Duration of diabetes was defined as time from the date of first discharge diagnosis or prescription redemption until the index date.

Covariates

To control for confounding from modifiable risk factors with a presumed association with diverticular disease,[2] we obtained data from DNHS on categories of body mass index (BMI) (underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9) or obese (≥30)), leisure time physical activity intensity (low, moderate or high),[22] smoking behaviour (current, former or never) and diet according to The Dietary Quality Score (healthy, reasonably healthy or unhealthy). The Dietary Quality Score, developed by the Research Centre for Prevention and Health, Denmark, was used as an aggregated dietary measure, categorising respondents based on their intake of fruit, vegetables, fish and saturated fat.[23]

In addition, as low socioeconomic status has been associated with an increased risk of diabetes and diverticular disease,[10 24] we obtained data on highest completed education as reported in the DNHS (compulsory only, currently studying, short, medium, long or other). Finally, we used the Civil Registration System and the DNHS to gather information on demographic factors, including survey year, sex and age, and additionally to ascertain death or emigration.

For descriptive purposes only, we included information on comorbidities and related medications possibly associated with diverticular disease.[1] We did not adjust for these as temporal ordering of these factors and diabetes may be difficult (ie, comorbidities may lie on the causal pathway from exposure to outcome). Diabetes has a gradual onset, and both pre-diabetes and type 2 diabetes are associated with increased risk of developing several of these comorbidities.[4 25] While we suspected similar difficulties regarding temporal ordering of the selected modifiable risk factors, these are likely stable over time,[26] and more likely to be precursors of the exposure (eg, obesity may contribute to the development of type 2 diabetes) than to be caused by the exposure.[4]

Diverticular disease

The primary outcome was an incident hospital diagnosis of diverticular disease. To identify incident events during follow-up, we searched the DNRP for primary or secondary inpatient or outpatient clinic discharge diagnoses of diverticular disease. The overall positive predictive value of the diverticular disease diagnosis in DNPR is estimated to be 98%, when measured against expert review of medical records.[27]

Secondary outcomes were chosen to reflect diverticulitis and included (1) incident surgically treated diverticular disease and (2) incident diverticular disease with an acute inpatient admission. As hospital-based diagnostic coding of diverticular disease inadequately predicts disease complications when used alone,[27] we based our definition of diverticulitis on a combination of ICD and NOMESCO surgery codes.

Statistical analyses

We characterised patients with type 2 diabetes and patients without diabetes according to the baseline covariates described above. Patients with type 2 diabetes were characterised overall and according to diabetes duration. Study participants contributed risk time from their age at the index date until their age at an incident diverticular disease event, death, emigration or 31 December 2018, whichever came first. Incidence rates and Cox regression model derived hazard ratios (HRs) with associated 95% CIs were calculated comparing patients with type 2 diabetes overall and stratified by diabetes duration, and patients without diabetes. We presented crude and adjusted HRs with age as the underlying time scale.[28] The adjusted models included survey year, sex, BMI, physical activity intensity, smoking behaviour, diet and education. We visually examined and verified the assumption of proportional hazards using log–log plots.

We performed several additional analyses. First, because patients with type 2 diabetes without hospital-based diagnosis of diabetes or a redeemed prescription for glucose-lowering medication are not captured by registry data,[25] we assembled an extended cohort of patients with type 2 diabetes also using self-reported data in the DNHS. In this analysis, we identified all patients with diabetes (based on registry data or self-report) and then excluded those with type 1 diabetes,[20] as described in the online supplemental material.

Second, because a diagnosis of type 2 diabetes may lead to increased diagnostic surveillance of other conditions,[4] including diverticular disease, we stratified DNHS respondents according to colonoscopy status (yes/no) before the index date. We used NOMESCO codes to identify patients with a previous colonoscopy.

Third, to explore the impact of missing values, we performed a complete case analysis restricting our study cohort to respondents without missing values for covariate data in the DNHS (BMI, physical activity intensity, smoking behaviour, diet and education).

Fourth, because type 2 diabetes may affect development of diverticulitis and thus discovery of the disease,[13] we repeated the analyses examining the secondary outcomes.

Fifth, as the prevalence of overweight and obesity varies between countries,[29] we stratified our results on BMI categories, to facilitate the interpretation of our results in other settings.

Finally, we calculated E-values for the main analyses. E-values represent the minimum magnitude of an association that an unmeasured confounder must have with both type 2 diabetes and diverticular disease to be able to explain the observed association.[30]

Online supplemental table 1 lists the ICD, ATC and NOMESCO codes that were used. Statistical analyses were performed using SAS software (V.9.4; SAS Institute).

Patient and public involvement

As the study was based on registry data patients or the public were not involved in the design or conduct of our research.

RESULTS

Patient characteristics

We identified 15 047 patients with type 2 diabetes and 210 606 patients without diabetes at the index date (table 1). Compared with patients without diabetes, patients with type 2 diabetes had a higher proportion of men (57% vs 46%) and individuals of at least 60 years of age (63% vs 42%). In addition, patients with type 2 diabetes had a higher burden of obesity (36% vs 14%) and low physical activity (28% vs 14%), but the differences regarding current smoking and unhealthy diet were negligible. As well, the proportion of individuals with compulsory education only was higher in patients with type 2 diabetes (22% vs 12%). Cardiovascular comorbidity and related medications were generally more prevalent among patients with diabetes. The degree of missingness of variables from DNHS was slightly higher among patients with type 2 diabetes compared with patients without diabetes.

The proportion of obese patients was slightly lower in patients with a longer duration of type 2 diabetes (34%) than among those with moderate (36%) and shorter duration (39%). The burden of comorbidities and comedications increased with increasing duration of type 2 diabetes.

Main analysis

We tallied 702 incident events with hospital-diagnosed diverticular disease during follow-up among patients with prevalent type 2 diabetes and 7825 among those without diabetes. This corresponded to incidence rates of 0.76 and 0.54 events per 1000 person years and a crude HR of 1.08 (95% CI 1.00 to 1.16). After adjustment, the HR was 0.88 (95% CI 0.80 to 0.96). Stepwise inclusion of the covariates in the regression model revealed that BMI was the main driver of this change in effect estimates (table 2).

The association clearly depended on diabetes duration (figure 2). The HR was lower among those with longer duration (adjusted HR: 0.76, 95% CI 0.67 to 0.87) than among those with moderate (adjusted HR: 0.94, 95% CI 0.78 to 1.12) and shorter (adjusted HR: 1.05, 95% CI 0.90 to 1.23) duration of type 2 diabetes (online supplemental table 2).

Additional analyses

Using both registry and self-report data to define type 2 diabetes yielded a result resembling that overall (adjusted HR: 0.93, 95% CI 0.85 to 1.00). When stratifying by colonoscopy status, HRs were similar to overall, with an adjusted HR of 0.80 (95% CI 0.64 to 1.01) in those with a previous colonoscopy (table 3). When stratifying by BMI category, HRs were similar to overall, with the exception of underweight, which included few individuals (table 3). In a complete case analysis, the crude HR was similar to the crude HR in the main analysis (crude HR: 1.03, 95% CI 0.94 to 1.13).

In analyses of secondary outcomes, we observed results comparable to the association in the main analysis for both surgically treated diverticular disease (adjusted HR: 0.93, 95% CI 0.65 to 1.34) and diverticular disease with an acute inpatient admission (adjusted HR: 0.89, 95% CI 0.71 to 1.12).

Finally, the E-value for the overall effect estimate was 1.53. It was 1.28 for patients with shorter duration of diabetes, 1.32 for moderate duration and 1.96 for those with longer duration.

DISCUSSION

Principal findings

In this cohort study of Danish adults ≥40 years of age, we found that patients with prevalent type 2 diabetes had a slightly lower risk of diverticular disease after covariate adjustment. BMI appeared to be the main driver of the change in effect estimates between crude and adjusted analyses. Finally, we found a duration–response relationship, as the observed association was more pronounced among patients with longer duration of diabetes.

Possible explanations

Two potential main mechanisms may explain our findings. One mechanism may be lifestyle modification, a cornerstone of type 2 diabetes treatment.[4] While the differences were small, we observed a decrease in the proportion of obese patients as the duration of diabetes increased. This may suggest that the BMI of patients with type 2 diabetes may decrease over time. While patients with type 2 diabetes still had a higher burden of obesity compared with patients without diabetes at the index date, lifestyle modification leading to reduction of BMI over time may contribute to a lowered risk of diverticular disease.

Another possible explanation for the observed association could be metformin treatment. Metformin is the preferred first-line treatment of type 2 diabetes in Denmark, with 72% of all persons using glucose-lowering drugs in 2014 being prescribed metformin.[31] A case-control study found that metformin use was associated with a lower risk of acute diverticulitis compared with other glucose lowering medications in diabetes (adjusted OR: 0.49, 95% CI 0.32 to 0.77).[32] However, this finding remains to be confirmed and thus, this potential explanation should be regarded highly speculative.

Comparison with previous studies

Our study largely agrees with the findings from Kopylov *et al*[9] and Nikberg *et al*[10] that also observed a lower risk of

Table 1 Characteristics of the 2010 and 2013 Danish National Health Survey (DNHS) respondents ≥40 years of age, with and without diabetes

	Type 2 diabetes				No diabetes
	Overall, n=15 047	Short duration, n=3927	Moderate duration, n=3200	Long duration, n=7920	Overall, n=210 606
DNHS survey year					
2010	7449 (49.5%)	2043 (52.0%)	1676 (52.4%)	3730 (47.1%)	115 230 (54.7%)
2013	7598 (50.5%)	1884 (48.0%)	1524 (47.6%)	4190 (52.9%)	95 376 (45.3%)
Age at index date, years					
Median (IQR)	67 (59.6–74.1)	66 (57.3–72.6)	67 (59.0–73.8)	68 (60.8–74.9)	59 (49.7–68.2)
40–59	3938 (26.2%)	1235 (31.4%)	891 (27.8%)	1812 (22.9%)	109 889 (52.2%)
60–79	9480 (63.0%)	2354 (59.9%)	1973 (61.7%)	5153 (65.1%)	87 755 (41.7%)
≥80	1629 (10.8%)	338 (8.6%)	336 (10.5%)	955 (12.1%)	12 962 (6.2%)
Sex					
Men	8606 (57.2%)	2243 (57.1%)	1790 (55.9%)	4573 (57.7%)	97 023 (46.1%)
Women	6441 (42.8%)	1684 (42.9%)	1410 (44.1%)	3347 (42.3%)	113 583 (53.9%)
BMI					
Underweight	100 (0.7%)	17 (0.4%)	24 (0.8%)	59 (0.7%)	3190 (1.5%)
Normal weight	3154 (21.0%)	743 (18.9%)	630 (19.7%)	1781 (22.5%)	93 281 (44.3%)
Overweight	5569 (37.0%)	1450 (36.9%)	1236 (38.6%)	2883 (36.4%)	78 241 (37.2%)
Obese	5388 (35.8%)	1524 (38.8%)	1153 (36.0%)	2711 (34.2%)	28 915 (13.7%)
Leisure time physical activity intensity					
Low	4170 (27.7%)	963 (24.5%)	827 (25.8%)	2380 (30.1%)	29 745 (14.1%)
Medium	9756 (64.8%)	2688 (68.4%)	2141 (66.9%)	4927 (62.2%)	169 640 (80.5%)
High	120 (0.8%)	37 (0.9%)	22 (0.7%)	61 (0.8%)	3672 (1.7%)
Smoking behaviour					
Current	3049 (20.3%)	807 (20.6%)	657 (20.5%)	1585 (20.0%)	44 328 (21.0%)
Former	6432 (42.7%)	1723 (43.9%)	1356 (42.4%)	3353 (42.3%)	74 549 (35.4%)
Never	4986 (33.1%)	1268 (32.3%)	1072 (33.5%)	2646 (33.4%)	86 711 (41.2%)
Diet					
Healthy	3145 (20.9%)	903 (23.0%)	682 (21.3%)	1560 (19.7%)	48 430 (23.0%)
Reasonably healthy	8939 (59.4%)	2325 (59.2%)	1917 (59.9%)	4697 (59.3%)	127 038 (60.3%)
Unhealthy	1695 (11.3%)	410 (10.4%)	351 (11.0%)	934 (11.8%)	24 721 (11.7%)
Highest completed education					
Compulsory only	3233 (21.5%)	789 (20.1%)	694 (21.7%)	1750 (22.1%)	26 192 (12.4%)
Studying	60 (0.4%)	14 (0.4%)	13 (0.4%)	33 (0.4%)	737 (0.3%)
Short	5306 (35.3%)	1462 (37.2%)	1097 (34.3%)	2747 (34.7%)	76 633 (36.4%)
Moderate	2842 (18.9%)	803 (20.4%)	624 (19.5%)	1415 (17.9%)	63 401 (30.1%)
Long	761 (5.1%)	195 (5.0%)	172 (5.4%)	394 (5.0%)	18 891 (9.0%)
Other	962 (6.4%)	236 (6.0%)	221 (6.9%)	505 (6.4%)	9946 (4.7%)
Comorbidities					
Myocardial infarction	684 (4.5%)	186 (4.7%)	153 (4.8%)	345 (4.4%)	2777 (1.3%)
Stroke	733 (4.9%)	169 (4.3%)	152 (4.8%)	412 (5.2%)	3690 (1.8%)
Heart failure	892 (5.9%)	208 (5.3%)	186 (5.8%)	498 (6.3%)	2606 (1.2%)
Hypertension	7423 (49.3%)	1655 (42.1%)	1478 (46.2%)	4290 (54.2%)	29 053 (13.8%)
Atrial fibrillation	1251 (8.3%)	317 (8.1%)	272 (8.5%)	662 (8.4%)	6144 (2.9%)
Comedications					
NSAIDs	1092 (7.3%)	270 (6.9%)	221 (6.9%)	601 (7.6%)	8339 (4.0%)
Antiplatelets	6693 (44.5%)	1381 (35.2%)	1283 (40.1%)	4029 (50.9%)	23 374 (11.1%)
ACEs/ARBs	7024 (46.7%)	1579 (40.2%)	1399 (43.7%)	4046 (51.1%)	25 458 (12.1%)

Continued

Table 1 Continued

	Type 2 diabetes				No diabetes
	Overall, n=15 047	Short duration, n=3927	Moderate duration, n=3200	Long duration, n=7920	Overall, n=210 606
Beta-blockers	4287 (28.5%)	1080 (27.5%)	885 (27.7%)	2322 (29.3%)	19 785 (9.4%)
Calcium channel blockers	4813 (32.0%)	1076 (27.4%)	914 (28.6%)	2823 (35.6%)	20 822 (9.9%)
Diuretics	5203 (34.6%)	1229 (31.3%)	1025 (32.0%)	2949 (37.2%)	24 453 (11.6%)
Statins	9976 (66.3%)	2352 (59.9%)	2111 (66.0%)	5513 (69.6%)	31 256 (14.8%)

Variables from DNHS are missing for some respondents with and without diabetes (BMI (836, 5.6% and 6979, 3.3%); leisure time physical activity intensity (1001, 6.7% and 7549, 3.6%); smoking behaviour (580, 3.9% and 5018, 2.4%); diet (1268, 8.4% and 10 417, 4.9%); and education (1883, 12.5% and 14 806, 7.0%)). Diabetes duration was defined as short (<2.5 years), moderate (2.5–4.9 years) and long (≥5 years).
ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30); NSAID, non-steroidal anti-inflammatory drug.

diverticular disease in patients with diabetes. Kopylov *et al*[9] adjusted for BMI and smoking and found a negative association between diabetes and diverticulosis (adjusted OR: 0.49, 95% CI 0.29 to 0.83). Nikberg *et al*[10] included adjustment for measures of socioeconomic status and found a negative association between diabetes and uncomplicated diverticular disease (adjusted HR: 0.79, 95% CI 0.74 to 0.84).

Our findings are at odds with those of Sakuta and Suzuki[6] which is the only previous study that clearly distinguished the exposed group as patients with type 2 diabetes. Their finding of higher prevalence rates of type 2 diabetes among middle-aged Japanese men with asymptomatic colonic diverticulum (22% vs 14% in those without) stands in contrast to our finding of a negative association. The potentially differing pathogenic mechanism of diverticular disease in oriental Asian populations compared with Western countries, with a distinct right-sided distribution of diverticula in the colon, may contribute to the observed difference,[33] in conjunction with lack of adjustment for modifiable risk factors.

Our finding of an increased risk of diverticular disease in prevalent type 2 diabetes in the crude regression model which changed to a decreased risk in the adjusted model may provide an explanation for the conflicting results of previous studies. None of the previous studies reporting an increased risk of diverticular disease in patients with diabetes[6–8] included adjustment for modifiable risk factors, including one study reporting an increased risk of diverticular disease in patients with a genetic liability to type 2 diabetes.[15] It is possible that the findings of these studies would have changed had they included adjustment for modifiable risk factors, most notably BMI. In fact, all studies suggesting that diabetes decreased or had no impact on the risk of diverticular disease included a measure of at least BMI,[9 11–14] with the exception of Nikberg *et al*[10]

Another possible explanation for the ambiguous association is that diabetes may not be associated with the formation of diverticula per se, but can affect complication occurrence and thus the discovery of the disease.[5 13] However, our finding of results comparable to the association in the main analysis for surgically treated diverticular disease and diverticular disease with an acute inpatient admission suggests that discovery of the disease prior to occurrence of complications may not impact the association between type 2 diabetes and diverticular disease, as these outcomes most likely are not affected by diagnostic surveillance. Our findings are in line with those from Jiang *et al*[34] where diabetes was associated with a lower risk of surgical intervention in diverticulitis (adjusted OR: 0.69, 95% CI 0.64 to 0.75). In addition, among patients with a colonoscopy prior to the index date we found an association similar to that in the main analysis, which may suggest that diagnostic surveillance does not impact our findings, despite diverticulosis often being asymptomatic and often diagnosed by colonoscopy.[27]

Strengths and limitations

Strengths of the current study include the use of nationwide registries in a free tax-supported healthcare system to ascertain hospital-based diagnoses and redeemed prescriptions.[35 36] This minimised the risk of bias resulting from differences in factors such as access to healthcare and socioeconomic status.

The use of registry data with high positive predictive values to identify both type 2 diabetes and diverticular disease is another strength. The exposed group included patients with type 2 diabetes treated both in the general practice and hospital sectors,[21] and the use of survey data allowed us to define patients with type 2 diabetes not captured by registry data in an extended exposure definition.[25] However, the cohort may still have included some patients misclassified as type 2 diabetes patients, such as those with late-onset type 1 diabetes. Furthermore, the ascertainment of modifiable risk factors was based on self-reporting and thus susceptible to information bias and bias from missing values. Nevertheless, any misclassification of exposure or covariates should be non-differential with respect to diverticular disease and bias our estimates towards the null. Our complete case analysis may suggest the impact of missing values was limited. The outcome of a discharge diagnosis of diverticular disease reflects patients who seek medical attention; therefore,

Table 2 Risk of diverticular disease in type 2 diabetes (no diabetes is the reference)

	HRs (95% CI)					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Type 2 diabetes	1.07 (0.99 to 1.16)	0.93 (0.86 to 1.01)	1.03 (0.95 to 1.11)	1.05 (0.97 to 1.14)	1.07 (0.98 to 1.16)	1.04 (0.96 to 1.13)

Stepwise regression models adjusting for age, sex, body mass index, physical activity intensity, smoking behaviour, diet and education.
Model 1: adjusted for age, sex and survey year.
Model 2: adjusted for covariates included in model one plus body mass index.
Model 3: adjusted for covariates included in model one plus leisure time physical activity intensity.
Model 4: adjusted for covariates included in model one plus smoking behaviour.
Model 5: adjusted for covariates included in model one plus diet.
Model 6: adjusted for covariates included in model one plus education.

Figure 2 Risk of diverticular disease in type 2 diabetes (no diabetes is the reference), overall and stratified by duration of diabetes. Estimates were calculated with the use of Cox proportional-hazards models with age as the underlying time scale, and after adjustment for survey year, sex, body mass index, physical activity intensity, smoking behaviour, diet and education.

the observed association is between type 2 diabetes and symptomatic diverticular disease. This may strengthen the clinical relevance of our results, while limiting the generalisability to asymptomatic diverticular disease. One additional limitation of the current study is that it may be affected by bias from depletion of susceptibles.[37] Should the modifiable risk factors or pre-diabetes increase the risk of diverticular disease prior to a diagnosis of type 2 diabetes, susceptible individuals may have been censored prior to inclusion in the cohort, which could bias the results towards a lower risk in diabetes. This source of bias is difficult to address when the exposure is a disease with an insidious onset; consequently, prior studies may also have suffered this limitation. Finally, we cannot rule out the possibility of unmeasured confounding. However, the observed E-values ranging between 1.28 and 1.96 indicate that our findings were robust to effects of unmeasured confounding.

CONCLUSIONS

In summary, we found that patients with type 2 diabetes had a higher incidence rate of diverticular disease compared with patients without diabetes. However, after adjustment for modifiable risk factors, type 2 diabetes appeared to be associated with a slightly lower risk of diverticular disease. The association was most pronounced among patients with a diabetes duration of at least 5 years. BMI appeared to be the main driver of the change in effect estimates

Table 3 Risk of diverticular disease in type 2 diabetes (no diabetes is the reference), stratified by colonoscopy status and body mass index category

	Events	Incidence rates per 1000 person years (95% CI)	HRs (95% CI) Crude*	HRs (95% CI) Adjusted†
Colonoscopy before index date				
Colonoscopy, No diabetes	1037	1.16 (1.09 to 1.23)	Reference	Reference
Colonoscopy, type 2 diabetes	119	1.37 (1.15 to 1.64)	1.02 (0.84 to 1.23)	0.80 (0.64 to 1.01)
No colonoscopy, no diabetes	6788	0.50 (0.49 to 0.51)	Reference	Reference
No colonoscopy, type 2 diabetes	582	0.69 (0.64 to 0.75)	1.06 (0.98 to 1.16)	0.87 (0.79 to 0.97)
Body mass index category				
Underweight, no diabetes	77	0.39 (0.31 to 0.49)	Reference	Reference
Underweight, type 2 diabetes	<5	0.79 (0.30 to 2.11)	1.71 (0.62 to 4.68)	2.23 (0.80 to 6.19)
Normal weight, no diabetes	2852	0.44 (0.42 to 0.46)	Reference	Reference
Normal weight, type 2 diabetes	116	0.62 (0.51 to 0.74)	1.02 (0.84 to 1.22)	0.95 (0.77 to 1.18)
Overweight, no diabetes	3238	0.60 (0.58 to 0.62)	Reference	Reference
Overweight, type 2 diabetes	245	0.71 (0.62 to 0.80)	0.88 (0.78 to 1.01)	0.82 (0.71 to 0.96)
Obese, no diabetes	1420	0.72 (0.68 to 0.76)	Reference	Reference
Obese, type 2 diabetes	286	0.84 (0.75 to 0.94)	0.95 (0.84 to 1.08)	0.91 (0.79 to 1.05)

*With age as underlying time variable.
†Based on the crude model with additional adjustment for survey year, sex, body mass index, physical activity intensity, smoking behaviour, diet and education.

between crude and adjusted analyses. Thus, lack of adjustment for this modifiable risk factor may partially explain the conflicting findings of previous studies.

Contributors FW, NS, KB, LP, LS, RE and HTS contributed to the design of the study. OE and HTS acquired the data. FW, NS, LP, RE and HTS directed the analyses, which was carried out by LP. FW wrote the initial draft. All authors contributed to the discussion and interpretation of the results, which secured the intellectual content of the manuscript. All authors accepted the final version for submission. HTS is the guarantor of the article.

Funding The present study was funded by a grant from the Novo Nordisk Foundation (NNF19OC0058609). LS was supported by a grant from the National Institutes of Health/National Institutes of Diabetes and Digestive and Kidney Diseases (R01DK101495). The Danish National Health Survey was funded by The Capital Region, Region Zealand, The South Denmark Region, The Central Denmark Region, The North Denmark Region, Ministry of Health and the National Institute of Public Health, University of Southern Denmark.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Data was accessed at secure servers and cannot be shared due to Danish legislation.

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SUPPLEMENTAL MATERIAL

Type 2 diabetes and risk of diverticular disease: a Danish cohort study

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Supplemental Material 1. Extended type 2 diabetes cohort

For this analysis, any type of diabetes was defined by at least one of the following three criteria: 1) self-reported diabetes diagnosis in the Danish National Health Survey (yes/no), 2) a hospital-based discharge diagnosis of diabetes registered in the Danish National Patient Registry before the index date, or 3) a redeemed prescription for a glucose-lowering drug registered in the Danish National Health Service Prescription Database before the index date. We then defined and excluded patients with type 1 diabetes as those with a hospital-based diabetes diagnosis or a redeemed prescription for insulin before 30 years of age and with no redeemed prescription of oral glucose-lowering medications before the index date.

Supplemental Table 1. *International Classification of Diseases (ICD), Nordic Medico-Statistical Committee System* (NOMESCO), and *Anatomical Therapeutic Chemical Classification System (ATC)* codes used in the study.

	ICD-10/NOMESCO	**ATC**
Exposure		
Type 2 Diabetes Mellitus	E10-E14 O24 (except O24.4) G63.2, H36.0, N08.3 **Type 2 diabetes mellitus**: first ICD-10 code or glucose-lowering medication (A10) at or above 40 years of age. **Subclassifications**: Type 1 diabetes mellitus: first ICD-10 code before 30 years of age and treated with insulin (A10A), in addition no history of oral glucose-lowering medications (A10B) before index date.	Insulin: A10A, and oral glucose-lowering medications: A10B
Outcome		
Diverticular Disease	K57.2–K57.9 (also used for exclusion) **Subclassifications**: 1) Surgically treated: ICD-10 code and a KJF, KJG, or KJAH01 surgery code (NOMESCO) recorded within 30 days after ICD-10 code. 2) Acute admission to inpatient care: ICD-10 code as an acute inpatient diagnosis	
Exclusion criteria		
Inflammatory Bowel Disease	K50-K51	
Colorectal Cancer	C18, C20	
Colonoscopy definition		
Colonoscopy or sigmoidoscopy (with or without biopsy)	KUJF32, KUJF35, KUJF42, KUJF45	
Comorbidities		
Myocardial Infarction	I21	
Stroke	I60, I61, I63, I64	
Heart Failure	I50, I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.8, I42.9	
Hypertension	I10-I15	Anti-hypertensive drugs: C02, vasodilators: C04, β-blockers: C07, calcium channel blockers: C08, renin-angiotensin system inhibitors: C09, and diuretics: C03 (≥2 prescriptions in the last year)
Atrial Fibrillation	I48	
Comedications		
Non-Steroidal Anti-Inflammatory Drugs		M01A (≥4 in the last year)
Antiplatelets		N02BA01, B01AC, (≥2 in the last year)

Angiotensin-Converting Enzyme inhibitors /Angiotensin 2 Receptor Blockers		C09AA, C09CA (≥2 in the last year)
Beta-Blockers		C07 (≥2 in the last year)
Calcium Channel Blockers		C08 (≥2 in the last year)
Diuretics		C03 (≥2 in the last year)
Statins		C10AA (≥2 in the last year)

Supplemental Table 2. Risk of diverticular disease in patients with and without diabetes among the 2010 and 2013 DNHS respondents ≥40 years of age, overall and stratified by duration of diabetes.

			Hazard ratios (95% CI)	
	Events	Incidence rates per 1,000 person-years (95% CI)	Crude*	Adjusted‡
No diabetes	7,825	0.54 (0.53-0.55)	Reference	Reference
Type 2 diabetes, overall	702	0.76 (0.70-0.82)	1.08 (1.00-1.16)	0.88 (0.80-0.96)
Short duration (< 2.5 years)	199	0.80 (0.70-0.92)	1.19 (1.04-1.37)	1.05 (0.90-1.23)
Moderate duration (2.5-4.9 years)	164	0.82 (0.70-0.95)	1.17 (1.00-1.37)	0.94 (0.78-1.12)
Long duration (≥ 5 years)	339	0.71 (0.64-0.79)	0.98 (0.88-1.09)	0.76 (0.67-0.87)

DNHS, Danish National Health Survey; **CI**, Confidence Interval.
*With age as underlying time variable. ‡Based on the crude model with additional adjustment for survey year, sex, body mass index, physical activity intensity, smoking behavior, diet, and education.