BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059852
Article Type:	Original research
Date Submitted by the Author:	03-Dec-2021
Complete List of Authors:	Wittström, Felix; Aarhus University Hospital, Department of Clinical Epidemiology Skajaa, Nils; Aarhus University Hospital, Department of Clinical Epidemiology Bonnesen, Kasper; Aarhus University Hospital, Department of Clinical Epidemiology Pedersen, Lars; Aarhus University Hospital, Department of Clinical Epidemiology Ekholm, Ola; University of Southern Denmark Strate, Lisa; University of Washington Medical School, Department of Medicine Erichsen, Rune; Aarhus University Hospital, Department of Clinical Epidemiology Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Adult gastroenterology < GASTROENTEROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Running head: Diabetes and diverticular disease

Authors:
Felix Wittström, MD;[1], Nils Skajaa, MSc;[1,2], Kasper Bonnesen, MD;[1], Lars Pedersen, PhD;[1], Ola Ekholm, MSc;[2], Lisa Strate, MD;[3], Rune Erichsen, PhD;[1], Henrik Toft Sørensen, DMSc[1]

Author affiliations:
[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark
[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[3]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, WA, USA

Address for correspondence:
Felix Wittström, MD
Department of Clinical Epidemiology, Aarhus University Hospital
Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark
Tel: +45 8716 7212 Email: fw@clin.au.dk

Word count: 3,460 (Max: 4,000) **Abstract word count:** 250 (Max: 300)

Guarantor of the article: Henrik Toft Sørensen, DMSc

ABSTRACT

Objective: We investigated the association between type 2 diabetes and risk of diverticular disease. Unlike previous studies, which have found conflicting results, we distinguished between diabetes types and adjusted for modifiable risk factors.

Design: We conducted a cohort study among respondents of the 2010 or the 2013 Danish National Health Survey which we followed until the end of 2018. There were 15,047 patients with type 2 diabetes and 210,606 patients without diabetes. We calculated incidence rates and hazard ratios (HRs), adjusted for survey year, sex, age, body mass index (BMI), physical activity intensity, smoking behavior, diet, and education, associating type 2 diabetes with an incident hospital diagnosis of diverticular disease. As physiological changes may develop gradually, 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 0.8 and 0.5 events per 1,000 person-years, corresponding to a crude HR of 1.08 (95% CI: 1.00-1.16) and an adjusted HR of 0.88 (95% CI: 0.80-0.96). The HR was lower among patients with ≥5 years duration of diabetes (adjusted HR: 0.76, 95% CI: 0.67-0.87) than among those with 2.5-4.9 years or <2.5 years duration.

Conclusion: We found prevalent type 2 diabetes to be associated with a lower risk of diverticular disease risk. We also found BMI to affect this association, and lack of adjustment for this modifiable risk factor may partially explain the conflicting findings of previous studies.

Keywords: Denmark, type 2 diabetes, diverticular disease, cohort study, modifiable risk factors

ARTICLE SUMMARY

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 both discerned type of diabetes studied and included adjustment for modifiable risk factors.

• We utilize 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 is 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 fiber 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 of 1.25 (95% confidence interval [CI]: 0.87-1.79), 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 (*e.g.* 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 fiber 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 December 31, 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, May 1st 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 upon 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 flowchart is provided in Figure 1.

As type 2 diabetes gradually contributes to physiological changes,[4] time spent with type 2 diabetes may affect the association with diverticular disease. We therefore stratified patients with type 2 diabetes into those with short (<2.5 years), moderate (2.5 - 4.9 years) and long (≥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 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 behavior (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, categorizing 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 (*i.e.* comorbidities may lie on the causal pathway from exposure to outcome). Diabetes has a gradual onset, and both prediabetes 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 (*e.g.* 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 characterized patients with type 2 diabetes and patients without diabetes according to the baseline covariates described above. Patients with type 2 diabetes were characterized 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 December 31, 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 behavior, diet, and education. We visually examined and verified the assumption of proportional hazards using log-log plots.

We performed several additional analyses. First, because type 2 diabetes patients 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 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 behavior, 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.

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.[29]

Supplemental Table 1 lists the ICD, ATC and NOMESCO codes that were used. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

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 diabetes patients. The degree of missingness of variables from DNHS was slightly higher among patients with type 2 diabetes compared to patients without diabetes.

The proportion of obese patients was slightly lower in patients with a long duration of type 2 diabetes (34%) than among those with moderate (36%) and short 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 7,825 among those without diabetes. This corresponded to incidence rates of 0.8 and 0.5 events per 1,000 person years and a crude HR of 1.08 (95% CI: 1.00-1.16). After adjustment, the HR was 0.88 (95% CI: 0.80-0.96). 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 long duration (adjusted HR: 0.76, 95% CI: 0.67-0.87) than among those with moderate (adjusted HR: 0.94, 95% CI: 0.78-1.12) and short (adjusted HR: 1.05, 95% CI: 0.90-1.23) duration of type 2 diabetes (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: 0.85-1.00). When stratifying by colonoscopy status, HRs were similar to overall, with an adjusted HR of 0.80 (95% CI: 0.64-1.01) in those with a previous colonoscopy (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: 0.94-1.13).

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: 0.65-1.34) and diverticular disease with an acute inpatient admission (adjusted HR: 0.89, 95% CI: 0.71-1.12).

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

DISCUSSION

Principal findings

In this cohort study of Danish adults ≥40 years of age, we found prevalent type 2 diabetes to be associated with a lower risk of diverticular disease risk. Additionally, we found that BMI affected the association between type 2 diabetes and diverticular disease. Finally, we found a duration-response relationship between type 2 diabetes and diverticular disease, 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 metformin treatment, the preferred first-line treatment of type 2 diabetes in Denmark.[30] A previous case-control study found that metformin was associated with lower risk of acute diverticulitis, compared with other glucose lowering medications in diabetes (adjusted OR: 0.49, 95% CI: 0.32-0.77).[31] Metformin has been suggested to ameliorate the effects of aging and to reduce organ degeneration, potentially through reducing insulin-like growth factor-1 levels.[32] As age is an important factor contributing to the development of diverticular disease,[1] the potential effect of metformin on aging processes may provide a feasible explanation for our finding.

Another possible explanation for the observed association could be lifestyle modification, a cornerstone of type 2 diabetes interventions.[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 can 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 decreasing BMI over time may contribute to a lowered risk of diverticular disease.

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 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: 0.29-0.83). 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: 0.74-0.84).

Our findings are at odds with those of Sakuta *et al.*[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 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: 0.64–0.75). 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 minimized the risk of bias resulting from differences in factors such as access to health care 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 type 2 diabetes patients 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, the observed association is between type 2 diabetes and symptomatic diverticular disease. This may strengthen the clinical relevance of our results, while limiting the generalizability to asymptomatic diverticular disease. Finally, we cannot rule out the possibility of unmeasured confounding. However, the observed E-values ranging between 1.28 and 1.96 indicates that our findings were robust to effects of unmeasured confounding.

Conclusions

In summary, we found prevalent type 2 diabetes to be associated with a lower risk of diverticular disease risk, most clearly observed among patients with a diabetes duration of at least 5 years. We also found BMI to affect this association, and lack of adjustment for this modifiable risk factor may partially explain the conflicting findings of previous studies.

Specific author contributions: FW, NS, KB, LP, 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.

Competing Interests: The authors have no conflicts of interest to declare. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Sources of funding: The present study was funded by Aarhus University and by a grant from the Novo Nordisk Foundation (NNF19OC0058609). Lisa Strate 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.

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

Ethics approval: The study was approved by the Danish Data Protection Agency (record number 2015-57-0002) and was due to use of registry data exempt from ethics committee review.

REFERENCES

1 Tursi A, Scarpignato C, Strate LL, *et al.* Colonic diverticular disease. *Nat Rev Dis Primer* 2020;6:20. doi:10.1038/s41572-020-0153-5

2 Strate LL, Morris AM. Epidemiology, Pathophysiology, and Treatment of Diverticulitis. *Gastroenterology* 2019;156:1282-1298.e1. doi:10.1053/j.gastro.2018.12.033

3 Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. *Nat Rev Endocrinol* 2012;8:228–36. doi:10.1038/nrendo.2011.183

4 DeFronzo RA, Ferrannini E, Groop L, *et al.* Type 2 diabetes mellitus. *Nat Rev Dis Primer* 2015;1:1–22. doi:10.1038/nrdp.2015.19

5 Lin X, Li J, Ying M, *et al.* Diabetes Increases Morbidities of Colonic Diverticular Disease and Colonic Diverticular Hemorrhage: A Systematic Review and Meta-Analysis. *Am J Ther* 2017;24:e213–21. doi:10.1097/MJT.0000000000000410

6 Sakuta H, Suzuki T. Prevalence rates of type 2 diabetes and hypertension are elevated among middle-aged Japanese men with colonic diverticulum. *Environ Health Prev Med* 2007;12:97–100. doi:10.1007/BF02898156

7 Braunschmid T, Stift A, Mittlböck M, *et al.* Constipation is not associated with diverticular disease – Analysis of 976 patients. *Int J Surg* 2015;19:42–5. doi:10.1016/j.ijsu.2015.04.045

8 Azzam N, Aljebreen AM, Alharbi O, *et al.* Prevalence and clinical features of colonic diverticulosis in a Middle Eastern population. *World J Gastrointest Endosc* 2013;5:391. doi:10.4253/wjge.v5.i8.391

9 Kopylov U, Ben-Horin S, Lahat A, *et al.* Obesity, metabolic syndrome and the risk of development of colonic diverticulosis. *Digestion* 2012;86:201–5. doi:10.1159/000339881

10 Nikberg M, Ji J, Leppert J, *et al.* Socioeconomic characteristics and comorbidities of diverticular disease in Sweden 1997-2012. *Int J Colorectal Dis* 2017;32:1591–6. doi:10.1007/s00384-017-2853-1

11 Song JH, Kim YS, Lee JH, *et al.* Clinical characteristics of colonic diverticulosis in Korea: a prospective study. *Korean J Intern Med* 2010;25:140–6. doi:10.3904/kjim.2010.25.2.140

12 Storz C, Rothenbacher T, Rospleszcz S, *et al.* Characteristics and associated risk factors of diverticular disease assessed by magnetic resonance imaging in subjects from a Western general population. *Eur Radiol* 2019;29:1094–103. doi:10.1007/s00330-018-5687-5

13 Tursi A, Violi A, Cambie' G, *et al.* Risk factors for endoscopic severity of diverticular disease of the colon and its outcome: a real-life case-control study. *Eur J Gastroenterol Hepatol* 2020;32:1123–9. doi:10.1097/MEG.0000000000001787

14 Crowe FL, Appleby PN, Allen NE, *et al.* Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *The BMJ* 2011;343:d4131. doi:10.1136/bmj.d4131

15 Yuan S, Larsson SC. Genetically Predicted Adiposity, Diabetes, and Lifestyle Factors in Relation to Diverticular Disease. *Clin Gastroenterol Hepatol* 2021;:S1542-3565(21)00641-8. doi:10.1016/j.cgh.2021.06.013

16 Christensen AI, Lau CJ, Kristensen PL, *et al.* The Danish National Health Survey: Study design, response rate and respondent characteristics in 2010, 2013 and 2017. *Scand J Public Health* 2020;:140349482096653. doi:10.1177/1403494820966534

17 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.

18 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90. doi:10.2147/CLEP.S91125

19 Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, *et al.* Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;4:303–13. doi:10.2147/CLEP.S37587

20 Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. *BMJ Open Diabetes Res Care* 2020;8. doi:10.1136/bmjdrc-2019-001071

21 Carstensen B, Kristensen JK, Marcussen MM, *et al.* The National Diabetes Register. *Scand J Public Health* 2011;39:58–61. doi:10.1177/1403494811404278

22 Grimby G, Börjesson M, Jonsdottir IH, *et al.* The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports* 2015;25 Suppl 4:119–25. doi:10.1111/sms.12611

23 Toft U, Kristoffersen LH, Lau C, *et al.* The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. *Eur J Clin Nutr* 2007;61:270–8. doi:10.1038/sj.ejcn.1602503

24 Tang KL, Rashid R, Godley J, *et al.* Association between subjective social status and cardiovascular disease and cardiovascular risk factors: a systematic review and meta-analysis. *BMJ Open* 2016;6:e010137. doi:10.1136/bmjopen-2015-010137

25 Jørgensen ME, Ellervik C, Ekholm O, *et al.* Estimates of prediabetes and undiagnosed type 2 diabetes in Denmark: The end of an epidemic or a diagnostic artefact? *Scand J Public Health* 2020;48:106–12. doi:10.1177/1403494818799606

26 Johansson SE, Sundquist J. Change in lifestyle factors and their influence on health status and all-cause mortality. *Int J Epidemiol* 1999;28:1073–80. doi:10.1093/ije/28.6.1073

27 Erichsen R, Strate L, Sørensen HT, *et al.* Positive predictive values of the International Classification of Disease, 10th edition diagnoses codes for diverticular disease in the Danish National Registry of Patients. *Clin Exp Gastroenterol* 2010;3:139–42. doi:10.2147/CEG.S13293

28 Cologne J, Hsu W-L, Abbott RD, *et al.* Proportional Hazards Regression in Epidemiologic Follow-up Studies: An Intuitive Consideration of Primary Time Scale. *Epidemiology* 2012;23:565–73. doi:10.1097/EDE.0b013e318253e418

29 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167:268–74. doi:10.7326/M16-2607

30 Christensen DH, Rungby J, Thomsen RW. Nationwide trends in glucose-lowering drug use, Denmark, 1999–2014. *Clin Epidemiol* 2016;8:381–7. doi:10.2147/CLEP.S113211

31 Freckelton J, Evans JA, Croagh D, *et al.* Metformin use in diabetics with diverticular disease is associated with reduced incidence of diverticulitis. *Scand J Gastroenterol* 2017;52:969–72. doi:10.1080/00365521.2017.1325930

32 Sunjaya AP, Sunjaya AF. Targeting ageing and preventing organ degeneration with metformin. *Diabetes Metab* 2021;47:101203. doi:10.1016/j.diabet.2020.09.009

33 Rajendra S, Ho JJ. Colonic diverticular disease in a multiracial Asian patient population has an ethnic predilection. *Eur J Gastroenterol Hepatol* 2005;17:871–5.

34 Jiang Y, Rodgers B, Damiris K, *et al.* The effects of diabetes mellitus on clinical outcomes of hospitalized patients with acute diverticulitis. *Eur J Gastroenterol Hepatol* Published Online First: 10 August 2020. doi:10.1097/MEG.0000000000001895

35 Schmidt M, Schmidt SAJ, Adelborg K, *et al.* The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:563–91. doi:10.2147/CLEP.S179083

36 Laugesen K, Ludvigsson JF, Schmidt M, *et al.* Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clin Epidemiol* 2021;13:533–54. doi:10.2147/CLEP.S314959

FIGURES AND TABLES

Figure 1. Study flowchart.

Table 1. Characteristics of the 2010 and 2013 DNHS respondents ≥40 years of age, with and without diabetes.

	Type 2 diabetes				No diabetes
	Overall, n=15,047	**Short duration,** n=3,927	**Moderate duration,** n=3,200	**Long duration,** n=7,920	**Overall**, n=210,606
DNHS survey year					
2010	7,449 (49.5%)	2,043 (52.0%)	1,676 (52.4%)	3,730 (47.1%)	115,230 (54.7%)
2013	7,598 (50.5%)	1,884 (48.0%)	1,524 (47.6%)	4,190 (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	3,938 (26.2%)	1,235 (31.4%)	891 (27.8%)	1,812 (22.9%)	109,889 (52.2%)
60-79	9,480 (63.0%)	2,354 (59.9%)	1,973 (61.7%)	5,153 (65.1%)	87,755 (41.7%)
≥80	1,629 (10.8%)	338 (8.6%)	336 (10.5%)	955 (12.1%)	12,962 (6.2%)
Sex					
Men	8,606 (57.2%)	2,243 (57.1%)	1,790 (55.9%)	4,573 (57.7%)	97,023 (46.1%)
Women	6,441 (42.8%)	1,684 (42.9%)	1,410 (44.1%)	3,347 (42.3%)	113,583 (53.9%)
BMI					
Underweight	100 (0.7%)	17 (0.4%)	24 (0.8%)	59 (0.7%)	3,190 (1.5%)
Normal weight	3,154 (21.0%)	743 (18.9%)	630 (19.7%)	1,781 (22.5%)	93,281 (44.3%)
Overweight	5,569 (37.0%)	1,450 (36.9%)	1,236 (38.6%)	2,883 (36.4%)	78,241 (37.2%)
Obese	5,388 (35.8%)	1,524 (38.8%)	1,153 (36.0%)	2,711 (34.2%)	28,915 (13.7%)
Leisure time physical activity intensity					
Low	4,170 (27.7%)	963 (24.5%)	827 (25.8%)	2,380 (30.1%)	29,745 (14.1%)
Medium	9,756 (64.8%)	2,688 (68.4%)	2,141 (66.9%)	4,927 (62.2%)	169,640 (80.5%)
High	120 (0.8%)	37 (0.9%)	22 (0.7%)	61 (0.8%)	3,672 (1.7%)
Smoking behavior					
Current	3,049 (20.3%)	807 (20.6%)	657 (20.5%)	1,585 (20.0%)	44,328 (21.0%)
Former	6,432 (42.7%)	1,723 (43.9%)	1,356 (42.4%)	3,353 (42.3%)	74,549 (35.4%)
Never	4,986 (33.1%)	1,268 (32.3%)	1,072 (33.5%)	2,646 (33.4%)	86,711 (41.2%)
Diet					
Healthy	3,145 (20.9%)	903 (23.0%)	682 (21.3%)	1,560 (19.7%)	48,430 (23.0%)
Reasonably healthy	8,939 (59.4%)	2,325 (59.2%)	1,917 (59.9%)	4,697 (59.3%)	127,038 (60.3%)
Unhealthy	1,695 (11.3%)	410 (10.4%)	351 (11.0%)	934 (11.8%)	24,721 (11.7%)
Highest completed education					
Compulsory only	3,233 (21.5%)	789 (20.1%)	694 (21.7%)	1,750 (22.1%)	26,192 (12.4%)
Studying	60 (0.4%)	14 (0.4%)	13 (0.4%)	33 (0.4%)	737 (0.3%)

Short	5,306 (35.3%)	1,462 (37.2%)	1,097 (34.3%)	2,747 (34.7%)	76,633 (36.4%)
Moderate	2,842 (18.9%)	803 (20.4%)	624 (19.5%)	1,415 (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%)	9,946 (4.7%)
Comorbidities					
Myocardial infarction	684 (4.5%)	186 (4.7%)	153 (4.8%)	345 (4.4%)	2,777 (1.3%)
Stroke	733 (4.9%)	169 (4.3%)	152 (4.8%)	412 (5.2%)	3,690 (1.8%)
Heart failure	892 (5.9%)	208 (5.3%)	186 (5.8%)	498 (6.3%)	2,606 (1.2%)
Hypertension	7,423 (49.3%)	1,655 (42.1%)	1,478 (46.2%)	4,290 (54.2%)	29,053 (13.8%)
Atrial fibrillation	1,251 (8.3%)	317 (8.1%)	272 (8.5%)	662 (8.4%)	6,144 (2.9%)
Comedications					
NSAIDs	1,092 (7.3%)	270 (6.9%)	221 (6.9%)	601 (7.6%)	8,339 (4.0%)
Antiplatelets	6,693 (44.5%)	1,381 (35.2%)	1,283 (40.1%)	4,029 (50.9%)	23,374 (11.1%)
ACEs/ARBs	7,024 (46.7%)	1,579 (40.2%)	1,399 (43.7%)	4,046 (51.1%)	25,458 (12.1%)
Beta-blockers	4,287 (28.5%)	1,080 (27.5%)	885 (27.7%)	2,322 (29.3%)	19,785 (9.4%)
Calcium channel blockers	4,813 (32.0%)	1,076 (27.4%)	914 (28.6%)	2,823 (35.6%)	20,822 (9.9%)
Diuretics	5,203 (34.6%)	1,229 (31.3%)	1,025 (32.0%)	2,949 (37.2%)	24,453 (11.6%)
Statins	9,976 (66.3%)	2,352 (59.9%)	2,111 (66.0%)	5,513 (69.6%)	31,256 (14.8%)

DNHS, Danish National Health Survey; **IQR,** Interquartile Range; **BMI**, Body Mass Index (<18.5, 18.5-24.9, 25-29.9, ≥30); **NSAID**, Non-Steroidal Anti-Inflammatory Drug; **ACE/ARB**, Angiotensin-Converting Enzyme inhibitor/Angiotensin II Receptor Blocker.

Note: Variables from DNHS are missing for some respondents with and without diabetes (BMI [836, 5.6% and 6,979, 3.3%]; leisure time physical activity intensity [1,001, 6.7% and 7,549, 3.6%]; smoking behavior [580, 3.9% and 5,018, 2.4%]; diet [1,268, 8.4% and 10,417, 4.9%]; and education [1,883, 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).

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 behavior, diet, and education.

Table 2. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference). Stepwise regression models adjusting for age, sex, body mass index, physical activity intensity, smoking behavior, diet, and education.

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

CI, Confidence Interval.
Model 1: Adjusted for age, sex, and survey year.
Model 2: Adjusted for covariates included in model 1 plus body mass index.
Model 3: Adjusted for covariates included in model 1 plus leisure time physical activity intensity.
Model 4: Adjusted for covariates included in model 1 plus smoking behavior.
Model 5: Adjusted for covariates included in model 1 plus diet.
Model 6: Adjusted for covariates included in model 1 plus education.

Table 3. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference), stratified by colonoscopy status.

			Hazard ratios (95% CI)	
	Events	Incidence rates per 1,000 person-years (95% CI)	Crude*	Adjusted‡
Colonoscopy before index date				
Colonoscopy, No diabetes	1,037	1.16 (1.09-1.23)	Reference	Reference
Colonoscopy, Type 2 diabetes	119	1.37 (1.15-1.64)	1.02 (0.84-1.23)	0.80 (0.64-1.01)
No Colonoscopy, No diabetes	6,788	0.50 (0.49-0.51)	Reference	Reference
No Colonoscopy, Type 2 diabetes	582	0.69 (0.64-0.75)	1.06 (0.98-1.16)	0.87 (0.79-0.97)

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.

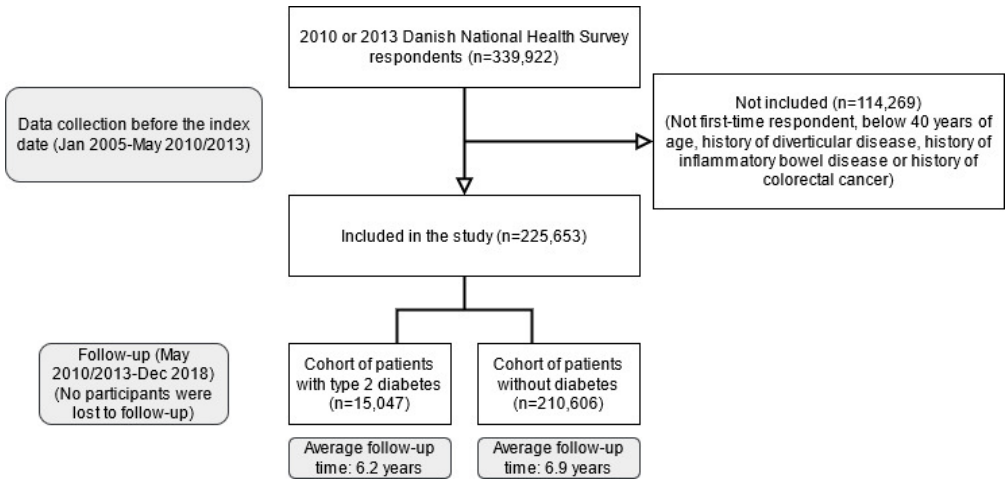

Figure 1. Study flowchart.

261x123mm (72 x 72 DPI)

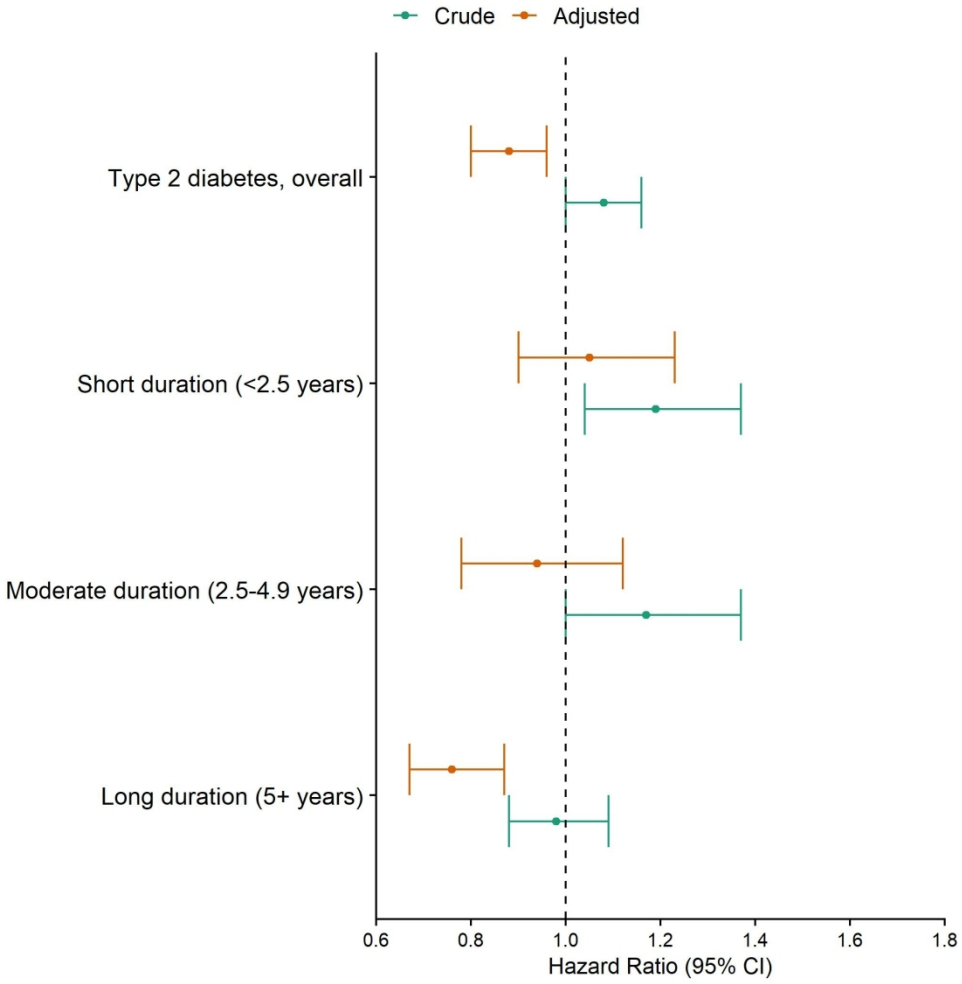

Figure 2. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference), overall and stratified by duration of diabetes. Estimates were calculated with the use of Cox proportional-hazards models with age as the underlying time scale, and after adjustment for survey year, sex, body mass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

177x177mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

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

Authors:

Felix Wittström, MD;[1], Nils Skajaa, MSc;[1,2], Kasper Bonnesen, MD;[1], Lars Pedersen, PhD;[1], Ola Ekholm, MSc;[2], Lisa Strate, MD;[3], Rune Erichsen, PhD;[1], Henrik Toft Sørensen, DMSc[1]

Author affiliations:

[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark

[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[3]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, WA, USA

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.

STROBE checklist for cohort study.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	Page 1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	Page 5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	#4	Present key elements of study design early in the paper	Page 7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	Page 7-8
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-11
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. Give information separately for exposed and unexposed groups if applicable.	Page 7-10
Bias	#9	Describe any efforts to address potential sources of bias	Page 8-11
Study size	#10	Explain how the study size was arrived at	Page 7

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 8-10
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	Page 10-11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	Page 10-11
Statistical methods	#12c	Explain how missing data were addressed	Page 11
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A (Page 7 & 16)
Statistical methods	#12e	Describe any sensitivity analyses	Page 10-11
Results			
Participants	#13a	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. Give information separately for exposed and unexposed groups if applicable.	Page 8
Participants	#13b	Give reasons for non-participation at each stage	Page 8
Participants	#13c	Consider use of a flow diagram	Page 8
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Page 12 & 24-25
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Page 24-25
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	Page 8
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Page 12 & 26
Main results	#16a	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	Page 12-13
Main results	#16b	Report category boundaries when continuous variables were categorized	N/A

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	Page 14
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.	Page 16-17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	Page 14-15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	Page 15-17
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	Page 1

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059852.R1
Article Type:	Original research
Date Submitted by the Author:	24-Jan-2022
Complete List of Authors:	Wittström, Felix; Aarhus University Hospital, Department of Clinical Epidemiology Skajaa, Nils; Aarhus University Hospital, Department of Clinical Epidemiology Bonnesen, Kasper; Aarhus University Hospital, Department of Clinical Epidemiology Pedersen, Lars; Aarhus University Hospital, Department of Clinical Epidemiology Ekholm, Ola; University of Southern Denmark Strate, Lisa; University of Washington Medical School, Department of Medicine Erichsen, Rune; Aarhus University Hospital, Department of Clinical Epidemiology Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Adult gastroenterology < GASTROENTEROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Running head: Diabetes and diverticular disease

Authors:
Felix Wittström, MD;[1], Nils Skajaa, MSc;[1,2], Kasper Bonnesen, MD;[1], Lars Pedersen, PhD;[1], Ola Ekholm, MSc;[2], Lisa Strate, MD;[3], Rune Erichsen, PhD;[1], Henrik Toft Sørensen, DMSc[1]

Author affiliations:
[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark
[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[3]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, WA, USA

Address for correspondence:
Felix Wittström, MD
Department of Clinical Epidemiology, Aarhus University Hospital
Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark
Tel: +45 8716 7212 Email: fw@clin.au.dk

Word count: 3,767 (Max: 4,000) **Abstract word count:** 276 (Max: 300)

Guarantor of the article: Henrik Toft Sørensen, DMSc

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 for incident hospital diagnosis of diverticular disease adjusted for survey year, sex, age, body mass index (BMI), physical activity intensity, smoking behavior, 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 1,000 person-years, corresponding to a crude HR of 1.08 (95% CI: 1.00-1.16) and an adjusted HR of 0.88 (95% CI: 0.80-0.96). The HR was lower among patients with ≥5 years duration of diabetes (adjusted HR: 0.76, 95% CI: 0.67-0.87) 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.

ARTICLE SUMMARY

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 utilize 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 is 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 fiber 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 of 1.25 (95% confidence interval [CI]: 0.87-1.79), 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 (*e.g.* 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 fiber 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 December 31, 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, May 1st 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 upon 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 flowchart 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 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 behavior (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, categorizing 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 (*i.e.* comorbidities may lie on the causal pathway from exposure to outcome). Diabetes has a gradual onset, and both prediabetes 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 (*e.g.* 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 characterized patients with type 2 diabetes and patients without diabetes according to the baseline covariates described above. Patients with type 2 diabetes were characterized 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 December 31, 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 behavior, diet, and education. We visually examined and verified the assumption of proportional hazards using log-log plots.

We performed several additional analyses. First, because type 2 diabetes patients 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 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 behavior, 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]

Supplemental Table 1 lists the ICD, ATC and NOMESCO codes that were used. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

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 diabetes patients. The degree of missingness of variables from DNHS was slightly higher among patients with type 2 diabetes compared to 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 7,825 among those without diabetes. This corresponded to incidence rates of 0.76 and 0.54 events per 1,000 person years and a crude HR of 1.08 (95% CI: 1.00-1.16). After adjustment, the HR was 0.88 (95% CI: 0.80-0.96). 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: 0.67-0.87) than among those with moderate (adjusted HR: 0.94, 95% CI: 0.78-1.12) and shorter (adjusted HR: 1.05, 95% CI: 0.90-1.23) duration of type 2 diabetes (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: 0.85-1.00). When stratifying by colonoscopy status, HRs were similar to overall, with an adjusted HR of 0.80 (95% CI: 0.64-1.01) 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: 0.94-1.13).

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: 0.65-1.34) and diverticular disease with an acute inpatient admission (adjusted HR: 0.89, 95% CI: 0.71-1.12).

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 metformin treatment, the preferred first-line treatment of type 2 diabetes in Denmark.[31] A previous case-control study found that metformin was associated with lower risk of acute diverticulitis, compared with other glucose lowering medications in diabetes (adjusted OR: 0.49, 95% CI: 0.32-0.77).[32] Metformin has been suggested to ameliorate the effects of aging and to reduce organ degeneration, potentially through reducing insulin-like growth factor-1 levels.[33] As age is an important factor contributing to the development of diverticular disease,[1] the potential effect of metformin on aging processes may provide a feasible explanation for our finding.

Another possible explanation for the observed association could be lifestyle modification, a cornerstone of type 2 diabetes interventions.[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 can 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 decreasing BMI over time may contribute to a lowered risk of diverticular disease.

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 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: 0.29-0.83). 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: 0.74-0.84).

Our findings are at odds with those of Sakuta *et al.*[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,[34] 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.*[35] where diabetes was associated with a lower risk of surgical intervention in diverticulitis (adjusted OR: 0.69, 95% CI: 0.64–0.75). 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.[36,37] This minimized the risk of bias resulting from differences in factors such as access to health care 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 type 2 diabetes patients 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, the observed association is between type 2 diabetes and symptomatic diverticular disease. This may strengthen the clinical relevance of our results, while limiting the generalizability to asymptomatic diverticular disease. One additional limitation of the current study is that it may be affected by bias from depletion of susceptibles.[38] Should the modifiable risk factors or prediabetes 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 indicates 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 between crude and adjusted analyses. Thus, lack of adjustment for this modifiable risk factor may partially explain the conflicting findings of previous studies.

Specific author contributions: 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.

Competing Interests: The authors have no conflicts of interest to declare. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Sources of funding: The present study was funded by a grant from the Novo Nordisk Foundation (NNF19OC0058609). Lisa Strate 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.

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

Ethics approval: The study was approved by the Danish Data Protection Agency (record number 2015-57-0002) and was due to use of registry data exempt from ethics committee review.

REFERENCES

1 Tursi A, Scarpignato C, Strate LL, *et al.* Colonic diverticular disease. *Nat Rev Dis Primer* 2020;**6**:20. doi:10.1038/s41572-020-0153-5

2 Strate LL, Morris AM. Epidemiology, Pathophysiology, and Treatment of Diverticulitis. *Gastroenterology* 2019;**156**:1282-1298.e1. doi:10.1053/j.gastro.2018.12.033

3 Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. *Nat Rev Endocrinol* 2012;**8**:228–36. doi:10.1038/nrendo.2011.183

4 DeFronzo RA, Ferrannini E, Groop L, *et al.* Type 2 diabetes mellitus. *Nat Rev Dis Primer* 2015;**1**:1–22. doi:10.1038/nrdp.2015.19

5 Lin X, Li J, Ying M, *et al.* Diabetes Increases Morbidities of Colonic Diverticular Disease and Colonic Diverticular Hemorrhage: A Systematic Review and Meta-Analysis. *Am J Ther* 2017;**24**:e213–21. doi:10.1097/MJT.0000000000000410

6 Sakuta H, Suzuki T. Prevalence rates of type 2 diabetes and hypertension are elevated among middle-aged Japanese men with colonic diverticulum. *Environ Health Prev Med* 2007;**12**:97–100. doi:10.1007/BF02898156

7 Braunschmid T, Stift A, Mittlböck M, *et al.* Constipation is not associated with diverticular disease – Analysis of 976 patients. *Int J Surg* 2015;**19**:42–5. doi:10.1016/j.ijsu.2015.04.045

8 Azzam N, Aljebreen AM, Alharbi O, *et al.* Prevalence and clinical features of colonic diverticulosis in a Middle Eastern population. *World J Gastrointest Endosc* 2013;**5**:391. doi:10.4253/wjge.v5.i8.391

9 Kopylov U, Ben-Horin S, Lahat A, *et al.* Obesity, metabolic syndrome and the risk of development of colonic diverticulosis. *Digestion* 2012;**86**:201–5. doi:10.1159/000339881

10 Nikberg M, Ji J, Leppert J, *et al.* Socioeconomic characteristics and comorbidities of diverticular disease in Sweden 1997-2012. *Int J Colorectal Dis* 2017;**32**:1591–6. doi:10.1007/s00384-017-2853-1

11 Song JH, Kim YS, Lee JH, *et al.* Clinical characteristics of colonic diverticulosis in Korea: a prospective study. *Korean J Intern Med* 2010;**25**:140–6. doi:10.3904/kjim.2010.25.2.140

12 Storz C, Rothenbacher T, Rospleszcz S, *et al.* Characteristics and associated risk factors of diverticular disease assessed by magnetic resonance imaging in subjects from a Western general population. *Eur Radiol* 2019;**29**:1094–103. doi:10.1007/s00330-018-5687-5

13 Tursi A, Violi A, Cambie' G, *et al.* Risk factors for endoscopic severity of diverticular disease of the colon and its outcome: a real-life case-control study. *Eur J Gastroenterol Hepatol* 2020;**32**:1123–9. doi:10.1097/MEG.0000000000001787

14 Crowe FL, Appleby PN, Allen NE, *et al.* Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *The BMJ* 2011;**343**:d4131. doi:10.1136/bmj.d4131

15 Yuan S, Larsson SC. Genetically Predicted Adiposity, Diabetes, and Lifestyle Factors in Relation to Diverticular Disease. *Clin Gastroenterol Hepatol* 2021;:S1542-3565(21)00641-8. doi:10.1016/j.cgh.2021.06.013

16 Christensen AI, Lau CJ, Kristensen PL, *et al.* The Danish National Health Survey: Study design, response rate and respondent characteristics in 2010, 2013 and 2017. *Scand J Public Health* 2020;:140349482096653. doi:10.1177/1403494820966534

17 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–9.

18 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–90. doi:10.2147/CLEP.S91125

19 Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, *et al.* Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;**4**:303–13. doi:10.2147/CLEP.S37587

20 Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. *BMJ Open Diabetes Res Care* 2020;**8**. doi:10.1136/bmjdrc-2019-001071

21 Carstensen B, Kristensen JK, Marcussen MM, *et al.* The National Diabetes Register. *Scand J Public Health* 2011;**39**:58–61. doi:10.1177/1403494811404278

22 Grimby G, Börjesson M, Jonsdottir IH, *et al.* The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports* 2015;**25 Suppl 4**:119–25. doi:10.1111/sms.12611

23 Toft U, Kristoffersen LH, Lau C, *et al.* The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. *Eur J Clin Nutr* 2007;**61**:270–8. doi:10.1038/sj.ejcn.1602503

24 Tang KL, Rashid R, Godley J, *et al.* Association between subjective social status and cardiovascular disease and cardiovascular risk factors: a systematic review and meta-analysis. *BMJ Open* 2016;**6**:e010137. doi:10.1136/bmjopen-2015-010137

25 Jørgensen ME, Ellervik C, Ekholm O, *et al.* Estimates of prediabetes and undiagnosed type 2 diabetes in Denmark: The end of an epidemic or a diagnostic artefact? *Scand J Public Health* 2020;**48**:106–12. doi:10.1177/1403494818799606

26 Johansson SE, Sundquist J. Change in lifestyle factors and their influence on health status and all-cause mortality. *Int J Epidemiol* 1999;**28**:1073–80. doi:10.1093/ije/28.6.1073

27 Erichsen R, Strate L, Sørensen HT, *et al.* Positive predictive values of the International Classification of Disease, 10th edition diagnoses codes for diverticular disease in the

Danish National Registry of Patients. *Clin Exp Gastroenterol* 2010;**3**:139–42. doi:10.2147/CEG.S13293

28 Cologne J, Hsu W-L, Abbott RD, *et al.* Proportional Hazards Regression in Epidemiologic Follow-up Studies: An Intuitive Consideration of Primary Time Scale. *Epidemiology* 2012;**23**:565–73. doi:10.1097/EDE.0b013e318253e418

29 NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet Lond Engl* 2016;**387**:1377–96. doi:10.1016/S0140-6736(16)30054-X

30 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;**167**:268–74. doi:10.7326/M16-2607

31 Christensen DH, Rungby J, Thomsen RW. Nationwide trends in glucose-lowering drug use, Denmark, 1999–2014. *Clin Epidemiol* 2016;**8**:381–7. doi:10.2147/CLEP.S113211

32 Freckelton J, Evans JA, Croagh D, *et al.* Metformin use in diabetics with diverticular disease is associated with reduced incidence of diverticulitis. *Scand J Gastroenterol* 2017;**52**:969–72. doi:10.1080/00365521.2017.1325930

33 Sunjaya AP, Sunjaya AF. Targeting ageing and preventing organ degeneration with metformin. *Diabetes Metab* 2021;**47**:101203. doi:10.1016/j.diabet.2020.09.009

34 Rajendra S, Ho JJ. Colonic diverticular disease in a multiracial Asian patient population has an ethnic predilection. *Eur J Gastroenterol Hepatol* 2005;**17**:871–5.

35 Jiang Y, Rodgers B, Damiris K, *et al.* The effects of diabetes mellitus on clinical outcomes of hospitalized patients with acute diverticulitis. *Eur J Gastroenterol Hepatol* Published Online First: 10 August 2020. doi:10.1097/MEG.0000000000001895

36 Schmidt M, Schmidt SAJ, Adelborg K, *et al.* The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;**11**:563–91. doi:10.2147/CLEP.S179083

37 Laugesen K, Ludvigsson JF, Schmidt M, *et al.* Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clin Epidemiol* 2021;**13**:533–54. doi:10.2147/CLEP.S314959

38 Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2020;**29**:1101–10. doi:10.1002/pds.5083

FIGURES AND TABLES

Figure 1. Study flowchart.

Table 1. Characteristics of the 2010 and 2013 DNHS respondents ≥40 years of age, with and without diabetes.

	Type 2 diabetes				No diabetes
	Overall, n=15,047	**Short duration,** n=3,927	**Moderate duration,** n=3,200	**Long duration,** n=7,920	**Overall**, n=210,606
DNHS survey year					
2010	7,449 (49.5%)	2,043 (52.0%)	1,676 (52.4%)	3,730 (47.1%)	115,230 (54.7%)
2013	7,598 (50.5%)	1,884 (48.0%)	1,524 (47.6%)	4,190 (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	3,938 (26.2%)	1,235 (31.4%)	891 (27.8%)	1,812 (22.9%)	109,889 (52.2%)
60-79	9,480 (63.0%)	2,354 (59.9%)	1,973 (61.7%)	5,153 (65.1%)	87,755 (41.7%)
≥80	1,629 (10.8%)	338 (8.6%)	336 (10.5%)	955 (12.1%)	12,962 (6.2%)
Sex					
Men	8,606 (57.2%)	2,243 (57.1%)	1,790 (55.9%)	4,573 (57.7%)	97,023 (46.1%)
Women	6,441 (42.8%)	1,684 (42.9%)	1,410 (44.1%)	3,347 (42.3%)	113,583 (53.9%)
BMI					
Underweight	100 (0.7%)	17 (0.4%)	24 (0.8%)	59 (0.7%)	3,190 (1.5%)
Normal weight	3,154 (21.0%)	743 (18.9%)	630 (19.7%)	1,781 (22.5%)	93,281 (44.3%)
Overweight	5,569 (37.0%)	1,450 (36.9%)	1,236 (38.6%)	2,883 (36.4%)	78,241 (37.2%)
Obese	5,388 (35.8%)	1,524 (38.8%)	1,153 (36.0%)	2,711 (34.2%)	28,915 (13.7%)
Leisure time physical activity intensity					
Low	4,170 (27.7%)	963 (24.5%)	827 (25.8%)	2,380 (30.1%)	29,745 (14.1%)
Medium	9,756 (64.8%)	2,688 (68.4%)	2,141 (66.9%)	4,927 (62.2%)	169,640 (80.5%)
High	120 (0.8%)	37 (0.9%)	22 (0.7%)	61 (0.8%)	3,672 (1.7%)
Smoking behavior					
Current	3,049 (20.3%)	807 (20.6%)	657 (20.5%)	1,585 (20.0%)	44,328 (21.0%)
Former	6,432 (42.7%)	1,723 (43.9%)	1,356 (42.4%)	3,353 (42.3%)	74,549 (35.4%)
Never	4,986 (33.1%)	1,268 (32.3%)	1,072 (33.5%)	2,646 (33.4%)	86,711 (41.2%)
Diet					
Healthy	3,145 (20.9%)	903 (23.0%)	682 (21.3%)	1,560 (19.7%)	48,430 (23.0%)
Reasonably healthy	8,939 (59.4%)	2,325 (59.2%)	1,917 (59.9%)	4,697 (59.3%)	127,038 (60.3%)
Unhealthy	1,695 (11.3%)	410 (10.4%)	351 (11.0%)	934 (11.8%)	24,721 (11.7%)
Highest completed education					
Compulsory only	3,233 (21.5%)	789 (20.1%)	694 (21.7%)	1,750 (22.1%)	26,192 (12.4%)
Studying	60 (0.4%)	14 (0.4%)	13 (0.4%)	33 (0.4%)	737 (0.3%)

Short	5,306 (35.3%)	1,462 (37.2%)	1,097 (34.3%)	2,747 (34.7%)	76,633 (36.4%)
Moderate	2,842 (18.9%)	803 (20.4%)	624 (19.5%)	1,415 (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%)	9,946 (4.7%)
Comorbidities					
Myocardial infarction	684 (4.5%)	186 (4.7%)	153 (4.8%)	345 (4.4%)	2,777 (1.3%)
Stroke	733 (4.9%)	169 (4.3%)	152 (4.8%)	412 (5.2%)	3,690 (1.8%)
Heart failure	892 (5.9%)	208 (5.3%)	186 (5.8%)	498 (6.3%)	2,606 (1.2%)
Hypertension	7,423 (49.3%)	1,655 (42.1%)	1,478 (46.2%)	4,290 (54.2%)	29,053 (13.8%)
Atrial fibrillation	1,251 (8.3%)	317 (8.1%)	272 (8.5%)	662 (8.4%)	6,144 (2.9%)
Comedications					
NSAIDs	1,092 (7.3%)	270 (6.9%)	221 (6.9%)	601 (7.6%)	8,339 (4.0%)
Antiplatelets	6,693 (44.5%)	1,381 (35.2%)	1,283 (40.1%)	4,029 (50.9%)	23,374 (11.1%)
ACEs/ARBs	7,024 (46.7%)	1,579 (40.2%)	1,399 (43.7%)	4,046 (51.1%)	25,458 (12.1%)
Beta-blockers	4,287 (28.5%)	1,080 (27.5%)	885 (27.7%)	2,322 (29.3%)	19,785 (9.4%)
Calcium channel blockers	4,813 (32.0%)	1,076 (27.4%)	914 (28.6%)	2,823 (35.6%)	20,822 (9.9%)
Diuretics	5,203 (34.6%)	1,229 (31.3%)	1,025 (32.0%)	2,949 (37.2%)	24,453 (11.6%)
Statins	9,976 (66.3%)	2,352 (59.9%)	2,111 (66.0%)	5,513 (69.6%)	31,256 (14.8%)

DNHS, Danish National Health Survey; **IQR,** Interquartile Range; **BMI**, Body Mass Index (<18.5, 18.5-24.9, 25-29.9, ≥30); **NSAID**, Non-Steroidal Anti-Inflammatory Drug; **ACE/ARB**, Angiotensin-Converting Enzyme inhibitor/Angiotensin II Receptor Blocker.

Note: Variables from DNHS are missing for some respondents with and without diabetes (BMI [836, 5.6% and 6,979, 3.3%]; leisure time physical activity intensity [1,001, 6.7% and 7,549, 3.6%]; smoking behavior [580, 3.9% and 5,018, 2.4%]; diet [1,268, 8.4% and 10,417, 4.9%]; and education [1,883, 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).

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 behavior, diet, and education.

Table 2. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference). Stepwise regression models adjusting for age, sex, body mass index, physical activity intensity, smoking behavior, diet, and education.

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

CI, Confidence Interval.
Model 1: Adjusted for age, sex, and survey year.
Model 2: Adjusted for covariates included in model 1 plus body mass index.
Model 3: Adjusted for covariates included in model 1 plus leisure time physical activity intensity.
Model 4: Adjusted for covariates included in model 1 plus smoking behavior.
Model 5: Adjusted for covariates included in model 1 plus diet.
Model 6: Adjusted for covariates included in model 1 plus education.

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

			Hazard ratios (95% CI)	
	Events	Incidence rates per 1,000 person-years (95% CI)	Crude*	Adjusted‡
Colonoscopy before index date				
Colonoscopy, No diabetes	1,037	1.16 (1.09-1.23)	Reference	Reference
Colonoscopy, Type 2 diabetes	119	1.37 (1.15-1.64)	1.02 (0.84-1.23)	0.80 (0.64-1.01)
No Colonoscopy, No diabetes	6,788	0.50 (0.49-0.51)	Reference	Reference
No Colonoscopy, Type 2 diabetes	582	0.69 (0.64-0.75)	1.06 (0.98-1.16)	0.87 (0.79-0.97)
Body mass index category				
Underweight, No diabetes	77	0.39 (0.31-0.49)	Reference	Reference
Underweight, Type 2 diabetes	<5	0.79 (0.30-2.11)	1.71 (0.62-4.68)	2.23 (0.80-6.19)
Normal weight, No diabetes	2,852	0.44 (0.42-0.46)	Reference	Reference
Normal weight, Type 2 diabetes	116	0.62 (0.51-0.74)	1.02 (0.84-1.22)	0.95 (0.77-1.18)
Overweight, No diabetes	3,238	0.60 (0.58-0.62)	Reference	Reference
Overweight, Type 2 diabetes	245	0.71 (0.62-0.80)	0.88 (0.78-1.01)	0.82 (0.71-0.96)
Obese, No diabetes	1,420	0.72 (0.68-0.76)	Reference	Reference
Obese, Type 2 diabetes	286	0.84 (0.75-0.94)	0.95 (0.84-1.08)	0.91 (0.79-1.05)

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.

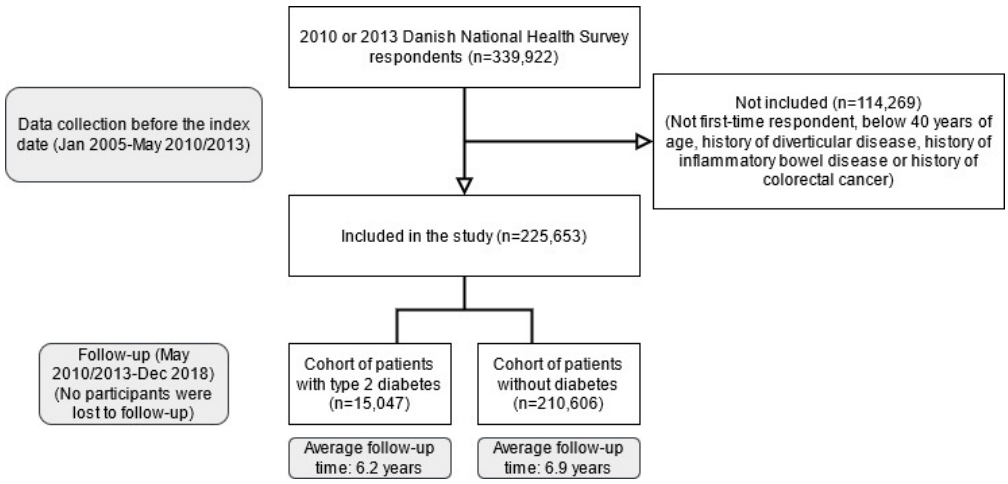

Figure 1. Study flowchart.

261x123mm (72 x 72 DPI)

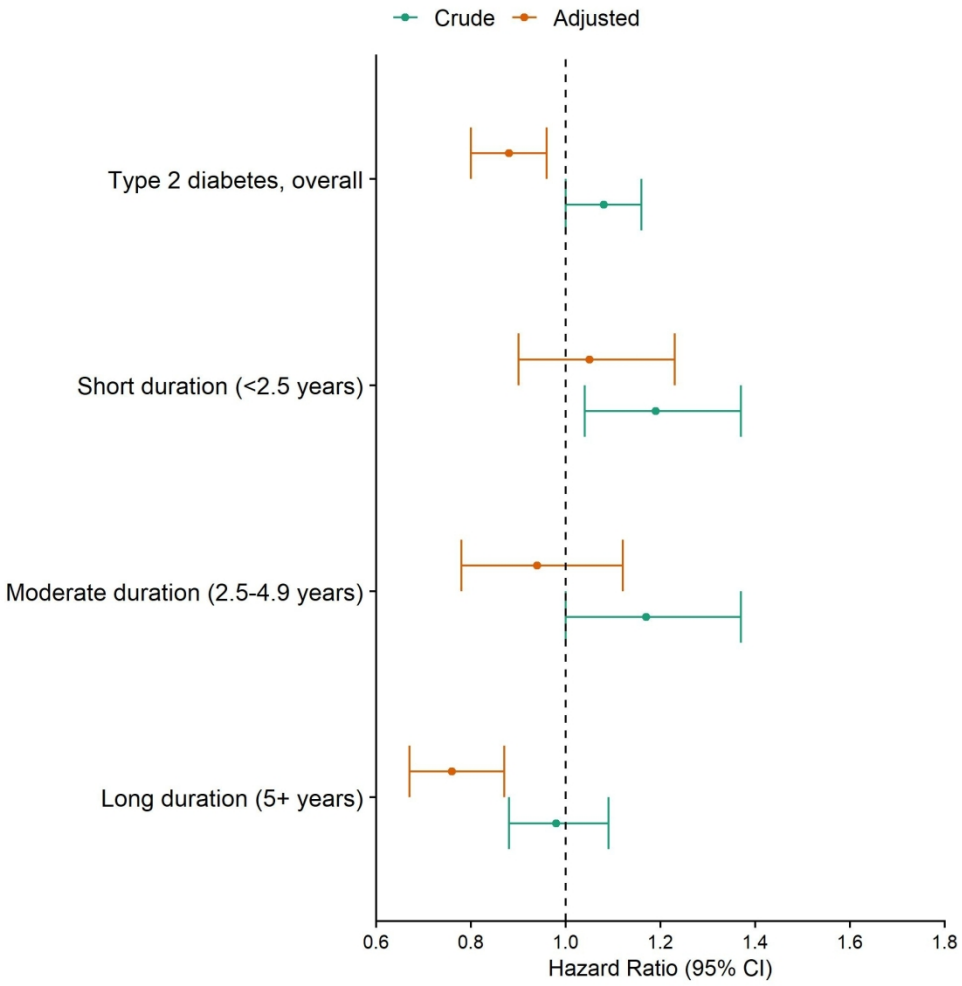

Figure 2. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference), overall and stratified by duration of diabetes. Estimates were calculated with the use of Cox proportional-hazards models with age as the underlying time scale, and after adjustment for survey year, sex, body mass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

177x177mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

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

Authors:

Felix Wittström, MD;[1], Nils Skajaa, MSc;[1,2], Kasper Bonnesen, MD;[1], Lars Pedersen, PhD;[1], Ola Ekholm, MSc;[2], Lisa Strate, MD;[3], Rune Erichsen, PhD;[1], Henrik Toft Sørensen, DMSc[1]

Author affiliations:

[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark

[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[3]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, WA, USA

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.

STROBE checklist for cohort study.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	Page 1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	Page 5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	#4	Present key elements of study design early in the paper	Page 7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	Page 7-8
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-11
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. Give information separately for exposed and unexposed groups if applicable.	Page 7-10
Bias	#9	Describe any efforts to address potential sources of bias	Page 8-11
Study size	#10	Explain how the study size was arrived at	Page 7

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 8-10
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	Page 10-11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	Page 10-11
Statistical methods	#12c	Explain how missing data were addressed	Page 11
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A (Page 7 & 24)
Statistical methods	#12e	Describe any sensitivity analyses	Page 10-11
Results			
Participants	#13a	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. Give information separately for exposed and unexposed groups if applicable.	Page 8 & 24
Participants	#13b	Give reasons for non-participation at each stage	Page 8 & 24
Participants	#13c	Consider use of a flow diagram	Page 24
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Page 13 & 25-26
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Page 25-26
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	Page 24
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Page 13-14
Main results	#16a	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	Page 13-14 & 27
Main results	#16b	Report category boundaries when continuous variables were categorized	N/A

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
Discussion			
Key results	#18	Summarise key results with reference to study objectives	Page 15
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.	Page 17-18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	Page 15-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	Page 15-17
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	Page 20

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059852.R2
Article Type:	Original research
Date Submitted by the Author:	01-Feb-2022
Complete List of Authors:	Wittström, Felix; Aarhus University Hospital, Department of Clinical Epidemiology Skajaa, Nils; Aarhus University Hospital, Department of Clinical Epidemiology Bonnesen, Kasper; Aarhus University Hospital, Department of Clinical Epidemiology Pedersen, Lars; Aarhus University Hospital, Department of Clinical Epidemiology Ekholm, Ola; University of Southern Denmark Strate, Lisa; University of Washington Medical School, Department of Medicine Erichsen, Rune; Aarhus University Hospital, Department of Clinical Epidemiology Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Adult gastroenterology < GASTROENTEROLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Running head: Diabetes and diverticular disease

Authors:
Felix Wittström, MD;[1], Nils Skajaa, MSc;[1,2], Kasper Bonnesen, MD;[1], Lars Pedersen, PhD;[1], Ola Ekholm, MSc;[2], Lisa Strate, MD;[3], Rune Erichsen, PhD;[1], Henrik Toft Sørensen, DMSc[1]

Author affiliations:
[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark
[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[3]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, WA, USA

Address for correspondence:
Felix Wittström, MD
Department of Clinical Epidemiology, Aarhus University Hospital
Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark
Tel: +45 8716 7212 Email: fw@clin.au.dk

Word count: 3,751 (Max: 4,000) **Abstract word count:** 276 (Max: 300)

Guarantor of the article: Henrik Toft Sørensen, DMSc

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 for incident hospital diagnosis of diverticular disease adjusted for survey year, sex, age, body mass index (BMI), physical activity intensity, smoking behavior, 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 1,000 person-years, corresponding to a crude HR of 1.08 (95% CI: 1.00-1.16) and an adjusted HR of 0.88 (95% CI: 0.80-0.96). The HR was lower among patients with ≥5 years duration of diabetes (adjusted HR: 0.76, 95% CI: 0.67-0.87) 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.

ARTICLE SUMMARY

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 utilize 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 is 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 fiber 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 of 1.25 (95% confidence interval [CI]: 0.87-1.79), 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 (*e.g.* 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 fiber 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 December 31, 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, May 1st 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 upon 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 flowchart 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 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 behavior (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, categorizing 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 (*i.e.* comorbidities may lie on the causal pathway from exposure to outcome). Diabetes has a gradual onset, and both prediabetes 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 (*e.g.* 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 characterized patients with type 2 diabetes and patients without diabetes according to the baseline covariates described above. Patients with type 2 diabetes were characterized 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 December 31, 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 behavior, diet, and education. We visually examined and verified the assumption of proportional hazards using log-log plots.

We performed several additional analyses. First, because type 2 diabetes patients 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 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 behavior, 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]

Supplemental Table 1 lists the ICD, ATC and NOMESCO codes that were used. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

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 diabetes patients. The degree of missingness of variables from DNHS was slightly higher among patients with type 2 diabetes compared to 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 7,825 among those without diabetes. This corresponded to incidence rates of 0.76 and 0.54 events per 1,000 person years and a crude HR of 1.08 (95% CI: 1.00-1.16). After adjustment, the HR was 0.88 (95% CI: 0.80-0.96). 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: 0.67-0.87) than among those with moderate (adjusted HR: 0.94, 95% CI: 0.78-1.12) and shorter (adjusted HR: 1.05, 95% CI: 0.90-1.23) duration of type 2 diabetes (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: 0.85-1.00). When stratifying by colonoscopy status, HRs were similar to overall, with an adjusted HR of 0.80 (95% CI: 0.64-1.01) 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: 0.94-1.13).

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: 0.65-1.34) and diverticular disease with an acute inpatient admission (adjusted HR: 0.89, 95% CI: 0.71-1.12).

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: 0.32-0.77).[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 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: 0.29-0.83). 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: 0.74-0.84).

Our findings are at odds with those of Sakuta *et al.*[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: 0.64–0.75). 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 minimized the risk of bias resulting from differences in factors such as access to health care 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 type 2 diabetes patients 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, the observed association is between type 2 diabetes and symptomatic diverticular disease. This may strengthen the clinical relevance of our results, while limiting the generalizability 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 prediabetes 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 indicates 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 between crude and adjusted analyses. Thus, lack of adjustment for this modifiable risk factor may partially explain the conflicting findings of previous studies.

Specific author contributions: 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.

Competing Interests: The authors have no conflicts of interest to declare. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Sources of funding: The present study was funded by a grant from the Novo Nordisk Foundation (NNF19OC0058609). Lisa Strate 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.

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

Ethics approval: The study was approved by the Danish Data Protection Agency (record number 2015-57-0002) and was due to use of registry data exempt from ethics committee review.

REFERENCES

1 Tursi A, Scarpignato C, Strate LL, *et al.* Colonic diverticular disease. *Nat Rev Dis Primer* 2020;**6**:20. doi:10.1038/s41572-020-0153-5

2 Strate LL, Morris AM. Epidemiology, Pathophysiology, and Treatment of Diverticulitis. *Gastroenterology* 2019;**156**:1282-1298.e1. doi:10.1053/j.gastro.2018.12.033

3 Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. *Nat Rev Endocrinol* 2012;**8**:228–36. doi:10.1038/nrendo.2011.183

4 DeFronzo RA, Ferrannini E, Groop L, *et al.* Type 2 diabetes mellitus. *Nat Rev Dis Primer* 2015;**1**:1–22. doi:10.1038/nrdp.2015.19

5 Lin X, Li J, Ying M, *et al.* Diabetes Increases Morbidities of Colonic Diverticular Disease and Colonic Diverticular Hemorrhage: A Systematic Review and Meta-Analysis. *Am J Ther* 2017;**24**:e213–21. doi:10.1097/MJT.0000000000000410

6 Sakuta H, Suzuki T. Prevalence rates of type 2 diabetes and hypertension are elevated among middle-aged Japanese men with colonic diverticulum. *Environ Health Prev Med* 2007;**12**:97–100. doi:10.1007/BF02898156

7 Braunschmid T, Stift A, Mittlböck M, *et al.* Constipation is not associated with diverticular disease – Analysis of 976 patients. *Int J Surg* 2015;**19**:42–5. doi:10.1016/j.ijsu.2015.04.045

8 Azzam N, Aljebreen AM, Alharbi O, *et al.* Prevalence and clinical features of colonic diverticulosis in a Middle Eastern population. *World J Gastrointest Endosc* 2013;**5**:391. doi:10.4253/wjge.v5.i8.391

9 Kopylov U, Ben-Horin S, Lahat A, *et al.* Obesity, metabolic syndrome and the risk of development of colonic diverticulosis. *Digestion* 2012;**86**:201–5. doi:10.1159/000339881

10 Nikberg M, Ji J, Leppert J, *et al.* Socioeconomic characteristics and comorbidities of diverticular disease in Sweden 1997-2012. *Int J Colorectal Dis* 2017;**32**:1591–6. doi:10.1007/s00384-017-2853-1

11 Song JH, Kim YS, Lee JH, *et al.* Clinical characteristics of colonic diverticulosis in Korea: a prospective study. *Korean J Intern Med* 2010;**25**:140–6. doi:10.3904/kjim.2010.25.2.140

12 Storz C, Rothenbacher T, Rospleszcz S, *et al.* Characteristics and associated risk factors of diverticular disease assessed by magnetic resonance imaging in subjects from a Western general population. *Eur Radiol* 2019;**29**:1094–103. doi:10.1007/s00330-018-5687-5

13 Tursi A, Violi A, Cambie' G, *et al.* Risk factors for endoscopic severity of diverticular disease of the colon and its outcome: a real-life case-control study. *Eur J Gastroenterol Hepatol* 2020;**32**:1123–9. doi:10.1097/MEG.0000000000001787

14 Crowe FL, Appleby PN, Allen NE, *et al.* Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *The BMJ* 2011;**343**:d4131. doi:10.1136/bmj.d4131

15 Yuan S, Larsson SC. Genetically Predicted Adiposity, Diabetes, and Lifestyle Factors in Relation to Diverticular Disease. *Clin Gastroenterol Hepatol* 2021;:S1542-3565(21)00641-8. doi:10.1016/j.cgh.2021.06.013

16 Christensen AI, Lau CJ, Kristensen PL, *et al.* The Danish National Health Survey: Study design, response rate and respondent characteristics in 2010, 2013 and 2017. *Scand J Public Health* 2020;:140349482096653. doi:10.1177/1403494820966534

17 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–9.

18 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–90. doi:10.2147/CLEP.S91125

19 Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, *et al.* Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;**4**:303–13. doi:10.2147/CLEP.S37587

20 Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. *BMJ Open Diabetes Res Care* 2020;**8**. doi:10.1136/bmjdrc-2019-001071

21 Carstensen B, Kristensen JK, Marcussen MM, *et al.* The National Diabetes Register. *Scand J Public Health* 2011;**39**:58–61. doi:10.1177/1403494811404278

22 Grimby G, Börjesson M, Jonsdottir IH, *et al.* The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports* 2015;**25 Suppl 4**:119–25. doi:10.1111/sms.12611

23 Toft U, Kristoffersen LH, Lau C, *et al.* The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. *Eur J Clin Nutr* 2007;**61**:270–8. doi:10.1038/sj.ejcn.1602503

24 Tang KL, Rashid R, Godley J, *et al.* Association between subjective social status and cardiovascular disease and cardiovascular risk factors: a systematic review and meta-analysis. *BMJ Open* 2016;**6**:e010137. doi:10.1136/bmjopen-2015-010137

25 Jørgensen ME, Ellervik C, Ekholm O, *et al.* Estimates of prediabetes and undiagnosed type 2 diabetes in Denmark: The end of an epidemic or a diagnostic artefact? *Scand J Public Health* 2020;**48**:106–12. doi:10.1177/1403494818799606

26 Johansson SE, Sundquist J. Change in lifestyle factors and their influence on health status and all-cause mortality. *Int J Epidemiol* 1999;**28**:1073–80. doi:10.1093/ije/28.6.1073

27 Erichsen R, Strate L, Sørensen HT, *et al.* Positive predictive values of the International Classification of Disease, 10th edition diagnoses codes for diverticular disease in the

Danish National Registry of Patients. *Clin Exp Gastroenterol* 2010;**3**:139–42. doi:10.2147/CEG.S13293

28 Cologne J, Hsu W-L, Abbott RD, *et al.* Proportional Hazards Regression in Epidemiologic Follow-up Studies: An Intuitive Consideration of Primary Time Scale. *Epidemiology* 2012;**23**:565–73. doi:10.1097/EDE.0b013e318253e418

29 NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet Lond Engl* 2016;**387**:1377–96. doi:10.1016/S0140-6736(16)30054-X

30 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;**167**:268–74. doi:10.7326/M16-2607

31 Christensen DH, Rungby J, Thomsen RW. Nationwide trends in glucose-lowering drug use, Denmark, 1999–2014. *Clin Epidemiol* 2016;**8**:381–7. doi:10.2147/CLEP.S113211

32 Freckelton J, Evans JA, Croagh D, *et al.* Metformin use in diabetics with diverticular disease is associated with reduced incidence of diverticulitis. *Scand J Gastroenterol* 2017;**52**:969–72. doi:10.1080/00365521.2017.1325930

33 Rajendra S, Ho JJ. Colonic diverticular disease in a multiracial Asian patient population has an ethnic predilection. *Eur J Gastroenterol Hepatol* 2005;**17**:871–5.

34 Jiang Y, Rodgers B, Damiris K, *et al.* The effects of diabetes mellitus on clinical outcomes of hospitalized patients with acute diverticulitis. *Eur J Gastroenterol Hepatol* Published Online First: 10 August 2020. doi:10.1097/MEG.0000000000001895

35 Schmidt M, Schmidt SAJ, Adelborg K, *et al.* The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;**11**:563–91. doi:10.2147/CLEP.S179083

36 Laugesen K, Ludvigsson JF, Schmidt M, *et al.* Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clin Epidemiol* 2021;**13**:533–54. doi:10.2147/CLEP.S314959

37 Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2020;**29**:1101–10. doi:10.1002/pds.5083

FIGURES AND TABLES

Figure 1. Study flowchart.

Table 1. Characteristics of the 2010 and 2013 DNHS respondents ≥40 years of age, with and without diabetes.

	Type 2 diabetes				No diabetes
	Overall, n=15,047	**Short duration,** n=3,927	**Moderate duration,** n=3,200	**Long duration,** n=7,920	**Overall**, n=210,606
DNHS survey year					
2010	7,449 (49.5%)	2,043 (52.0%)	1,676 (52.4%)	3,730 (47.1%)	115,230 (54.7%)
2013	7,598 (50.5%)	1,884 (48.0%)	1,524 (47.6%)	4,190 (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	3,938 (26.2%)	1,235 (31.4%)	891 (27.8%)	1,812 (22.9%)	109,889 (52.2%)
60-79	9,480 (63.0%)	2,354 (59.9%)	1,973 (61.7%)	5,153 (65.1%)	87,755 (41.7%)
≥80	1,629 (10.8%)	338 (8.6%)	336 (10.5%)	955 (12.1%)	12,962 (6.2%)
Sex					
Men	8,606 (57.2%)	2,243 (57.1%)	1,790 (55.9%)	4,573 (57.7%)	97,023 (46.1%)
Women	6,441 (42.8%)	1,684 (42.9%)	1,410 (44.1%)	3,347 (42.3%)	113,583 (53.9%)
BMI					
Underweight	100 (0.7%)	17 (0.4%)	24 (0.8%)	59 (0.7%)	3,190 (1.5%)
Normal weight	3,154 (21.0%)	743 (18.9%)	630 (19.7%)	1,781 (22.5%)	93,281 (44.3%)
Overweight	5,569 (37.0%)	1,450 (36.9%)	1,236 (38.6%)	2,883 (36.4%)	78,241 (37.2%)
Obese	5,388 (35.8%)	1,524 (38.8%)	1,153 (36.0%)	2,711 (34.2%)	28,915 (13.7%)
Leisure time physical activity intensity					
Low	4,170 (27.7%)	963 (24.5%)	827 (25.8%)	2,380 (30.1%)	29,745 (14.1%)
Medium	9,756 (64.8%)	2,688 (68.4%)	2,141 (66.9%)	4,927 (62.2%)	169,640 (80.5%)
High	120 (0.8%)	37 (0.9%)	22 (0.7%)	61 (0.8%)	3,672 (1.7%)
Smoking behavior					
Current	3,049 (20.3%)	807 (20.6%)	657 (20.5%)	1,585 (20.0%)	44,328 (21.0%)
Former	6,432 (42.7%)	1,723 (43.9%)	1,356 (42.4%)	3,353 (42.3%)	74,549 (35.4%)
Never	4,986 (33.1%)	1,268 (32.3%)	1,072 (33.5%)	2,646 (33.4%)	86,711 (41.2%)
Diet					
Healthy	3,145 (20.9%)	903 (23.0%)	682 (21.3%)	1,560 (19.7%)	48,430 (23.0%)
Reasonably healthy	8,939 (59.4%)	2,325 (59.2%)	1,917 (59.9%)	4,697 (59.3%)	127,038 (60.3%)
Unhealthy	1,695 (11.3%)	410 (10.4%)	351 (11.0%)	934 (11.8%)	24,721 (11.7%)
Highest completed education					
Compulsory only	3,233 (21.5%)	789 (20.1%)	694 (21.7%)	1,750 (22.1%)	26,192 (12.4%)
Studying	60 (0.4%)	14 (0.4%)	13 (0.4%)	33 (0.4%)	737 (0.3%)

Short	5,306 (35.3%)	1,462 (37.2%)	1,097 (34.3%)	2,747 (34.7%)	76,633 (36.4%)
Moderate	2,842 (18.9%)	803 (20.4%)	624 (19.5%)	1,415 (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%)	9,946 (4.7%)
Comorbidities					
Myocardial infarction	684 (4.5%)	186 (4.7%)	153 (4.8%)	345 (4.4%)	2,777 (1.3%)
Stroke	733 (4.9%)	169 (4.3%)	152 (4.8%)	412 (5.2%)	3,690 (1.8%)
Heart failure	892 (5.9%)	208 (5.3%)	186 (5.8%)	498 (6.3%)	2,606 (1.2%)
Hypertension	7,423 (49.3%)	1,655 (42.1%)	1,478 (46.2%)	4,290 (54.2%)	29,053 (13.8%)
Atrial fibrillation	1,251 (8.3%)	317 (8.1%)	272 (8.5%)	662 (8.4%)	6,144 (2.9%)
Comedications					
NSAIDs	1,092 (7.3%)	270 (6.9%)	221 (6.9%)	601 (7.6%)	8,339 (4.0%)
Antiplatelets	6,693 (44.5%)	1,381 (35.2%)	1,283 (40.1%)	4,029 (50.9%)	23,374 (11.1%)
ACEs/ARBs	7,024 (46.7%)	1,579 (40.2%)	1,399 (43.7%)	4,046 (51.1%)	25,458 (12.1%)
Beta-blockers	4,287 (28.5%)	1,080 (27.5%)	885 (27.7%)	2,322 (29.3%)	19,785 (9.4%)
Calcium channel blockers	4,813 (32.0%)	1,076 (27.4%)	914 (28.6%)	2,823 (35.6%)	20,822 (9.9%)
Diuretics	5,203 (34.6%)	1,229 (31.3%)	1,025 (32.0%)	2,949 (37.2%)	24,453 (11.6%)
Statins	9,976 (66.3%)	2,352 (59.9%)	2,111 (66.0%)	5,513 (69.6%)	31,256 (14.8%)

DNHS, Danish National Health Survey; **IQR,** Interquartile Range; **BMI**, Body Mass Index (<18.5, 18.5-24.9, 25-29.9, ≥30); **NSAID**, Non-Steroidal Anti-Inflammatory Drug; **ACE/ARB**, Angiotensin-Converting Enzyme inhibitor/Angiotensin II Receptor Blocker.

Note: Variables from DNHS are missing for some respondents with and without diabetes (BMI [836, 5.6% and 6,979, 3.3%]; leisure time physical activity intensity [1,001, 6.7% and 7,549, 3.6%]; smoking behavior [580, 3.9% and 5,018, 2.4%]; diet [1,268, 8.4% and 10,417, 4.9%]; and education [1,883, 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).

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 behavior, diet, and education.

Table 2. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference). Stepwise regression models adjusting for age, sex, body mass index, physical activity intensity, smoking behavior, diet, and education.

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

CI, Confidence Interval.
Model 1: Adjusted for age, sex, and survey year.
Model 2: Adjusted for covariates included in model 1 plus body mass index.
Model 3: Adjusted for covariates included in model 1 plus leisure time physical activity intensity.
Model 4: Adjusted for covariates included in model 1 plus smoking behavior.
Model 5: Adjusted for covariates included in model 1 plus diet.
Model 6: Adjusted for covariates included in model 1 plus education.

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

			Hazard ratios (95% CI)	
	Events	Incidence rates per 1,000 person-years (95% CI)	Crude*	Adjusted‡
Colonoscopy before index date				
Colonoscopy, No diabetes	1,037	1.16 (1.09-1.23)	Reference	Reference
Colonoscopy, Type 2 diabetes	119	1.37 (1.15-1.64)	1.02 (0.84-1.23)	0.80 (0.64-1.01)
No Colonoscopy, No diabetes	6,788	0.50 (0.49-0.51)	Reference	Reference
No Colonoscopy, Type 2 diabetes	582	0.69 (0.64-0.75)	1.06 (0.98-1.16)	0.87 (0.79-0.97)
Body mass index category				
Underweight, No diabetes	77	0.39 (0.31-0.49)	Reference	Reference
Underweight, Type 2 diabetes	<5	0.79 (0.30-2.11)	1.71 (0.62-4.68)	2.23 (0.80-6.19)
Normal weight, No diabetes	2,852	0.44 (0.42-0.46)	Reference	Reference
Normal weight, Type 2 diabetes	116	0.62 (0.51-0.74)	1.02 (0.84-1.22)	0.95 (0.77-1.18)
Overweight, No diabetes	3,238	0.60 (0.58-0.62)	Reference	Reference
Overweight, Type 2 diabetes	245	0.71 (0.62-0.80)	0.88 (0.78-1.01)	0.82 (0.71-0.96)
Obese, No diabetes	1,420	0.72 (0.68-0.76)	Reference	Reference
Obese, Type 2 diabetes	286	0.84 (0.75-0.94)	0.95 (0.84-1.08)	0.91 (0.79-1.05)

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.

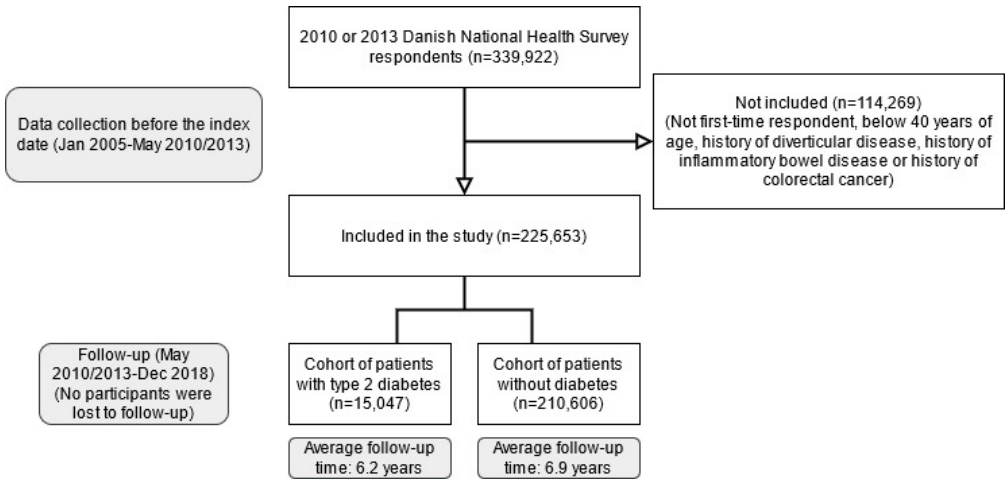

Figure 1. Study flowchart.

261x123mm (72 x 72 DPI)

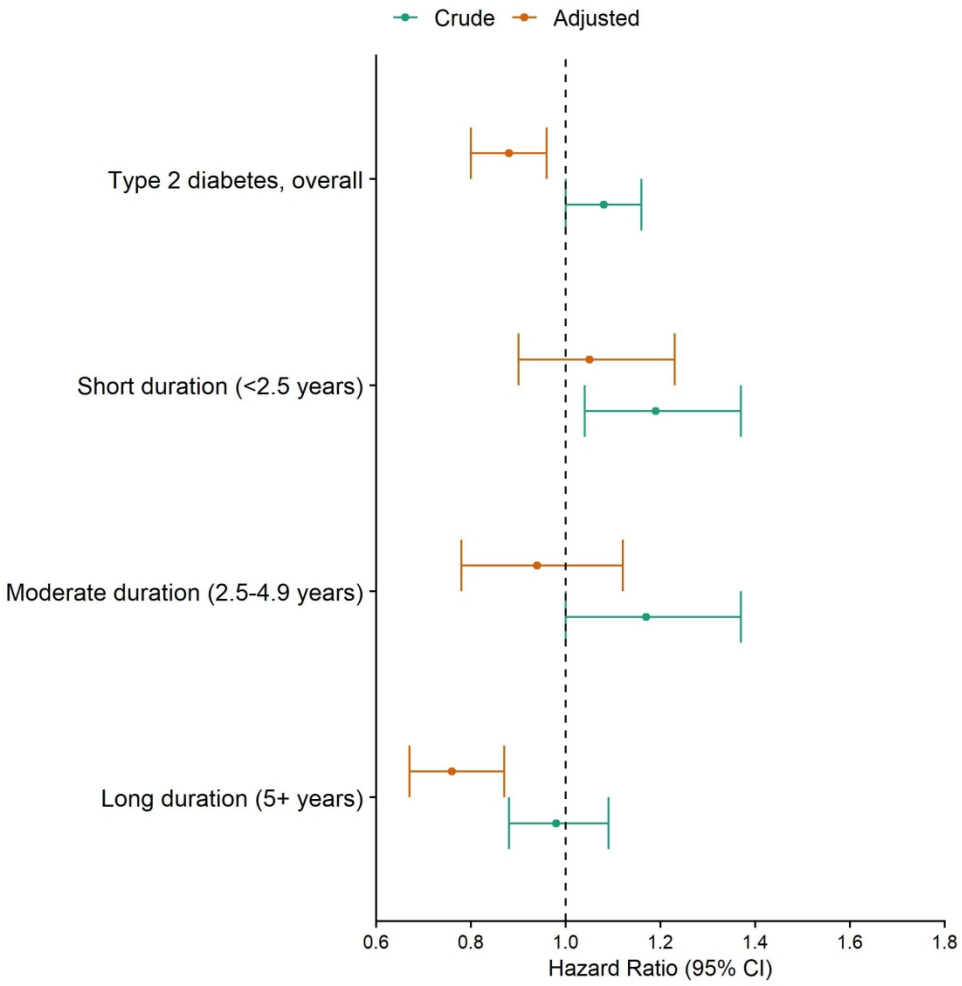

Figure 2. Risk of diverticular disease in type 2 diabetes (no diabetes is the reference), overall and stratified by duration of diabetes. Estimates were calculated with the use of Cox proportional-hazards models with age as the underlying time scale, and after adjustment for survey year, sex, body mass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

177x177mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

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

Authors:

Felix Wittström, MD;[1], Nils Skajaa, MSc;[1,2], Kasper Bonnesen, MD;[1], Lars Pedersen, PhD;[1], Ola Ekholm, MSc;[2], Lisa Strate, MD;[3], Rune Erichsen, PhD;[1], Henrik Toft Sørensen, DMSc[1]

Author affiliations:

[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark

[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[3]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, WA, USA

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.

STROBE checklist for cohort study.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	Page 1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	Page 5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	#4	Present key elements of study design early in the paper	Page 7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	Page 7-8
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-11
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. Give information separately for exposed and unexposed groups if applicable.	Page 7-10
Bias	#9	Describe any efforts to address potential sources of bias	Page 8-11
Study size	#10	Explain how the study size was arrived at	Page 7

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 8-10
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	Page 10-11
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	Page 10-11
Statistical methods	#12c	Explain how missing data were addressed	Page 11
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A (Page 7 & 24)
Statistical methods	#12e	Describe any sensitivity analyses	Page 10-11
Results			
Participants	#13a	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. Give information separately for exposed and unexposed groups if applicable.	Page 8 & 24
Participants	#13b	Give reasons for non-participation at each stage	Page 8 & 24
Participants	#13c	Consider use of a flow diagram	Page 24
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Page 13 & 25-26
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Page 25-26
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	Page 24
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Page 13-14
Main results	#16a	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	Page 13-14 & 27
Main results	#16b	Report category boundaries when continuous variables were categorized	N/A

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
Discussion			
Key results	#18	Summarise key results with reference to study objectives	Page 15
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.	Page 17-18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	Page 15-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	Page 15-17
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	Page 20