Statins and risk of diverticular disease

Nested case–control study

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Published in:
Pharmacoepidemiology and Drug Safety

DOI:
10.1002/pds.5205

Publication date:
2021

Document version:
Accepted manuscript

Citation for pulished version (APA):
Skajaa, N., Schønfeldt Troelsen, F., Pedersen, L., Ekholm, O., Strate, L. L., Erichsen, R., & Sørensen, H. T. (2021). Statins and risk of diverticular disease: Nested case–control study. *Pharmacoepidemiology and Drug Safety*, *30*(6), 770-778. https://doi.org/10.1002/pds.5205

Statins and risk of diverticular disease: Nested case-control study

Running head: Statins and diverticular disease

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

Word count: 3318

SUMMARY

Background: Statins exert pleiotropic anti-inflammatory effects and may prevent diverticular disease. However, the association remains poorly understood with previous studies obtaining conflicting results.

Aims: To examine the effect of statin on the subsequent risk of diverticular disease.

Methods: We conducted a nested case-control study in Denmark among respondents (>18 years) of the 2010 or the 2013 Danish National Health Survey. Among these, we identified 8,809 cases of hospital-diagnosed diverticular disease and risk-set sampled population controls without diverticular disease. Using complete prescription and hospital records, we used conditional logistic regression to compute odds ratios (ORs) associating statin use with diverticular disease. In adjusted analyses, we controlled for hospital-based diagnoses, medication use other than statins, and lifestyle and socioeconomic factors.

Results: The fully-adjusted OR for diverticular disease associated with ever use (≥1 statin prescription filling) was 1.19 (95% CI: 1.12–1.27) compared with never use. However, we observed no dose-response relation. For example, among short-term users (<5 years), the OR was 1.18 (95% CI: 1.04–1.35) for low intensity users and 1.13 (95% CI: 1.01–1.26) for high intensity users. Among long-term users (≥5 years), the respective ORs were 1.25 (95% CI: 1.13–1.38) and 1.11 (95% CI: 0.98–1.24). In analyses restricting to cases and controls with a previous colonoscopy, associations were null (OR: 1.01 [95% CI: 0.85-1.20]).

Conclusions: The observed association of a higher risk of diverticular disease associated with statins could be explained by diagnostic bias. Our study did not support a protective nor harmful effect of statins on the risk of diverticular disease.

Keywords: Statins, diverticular disease, nested case-control study.

KEY POINTS

- Statins possess pleiotropic anti-inflammatory effects and may prevent diverticular disease.
- To date, three studies have investigated the association between statins and diverticular disease obtaining contradictory results.
- In this large case-control analysis nested within a nationwide health survey, we found a slightly higher risk of diverticular disease associated with statin use, in contrast to what we expected.
- However, a lack of a dose-response relation and the presence of diagnostic bias indicate that the association is not causal.
- Our study did not support a protective nor harmful effect of statins on the risk of diverticular disease

INTRODUCTION

Diverticular disease, including diverticulitis and diverticulosis, is a common gastrointestinal disorder in the Western world.[1, 2] The prevalence increases steeply with age, affecting up to 60% of adults aged 60 years and older.[1, 2] The condition remains asymptomatic in most patients, but around 5% develop diverticulitis that can lead to complications such as bowel obstruction, abscess, or perforation.[3] Almost 2 million outpatient visits and 200,000 emergency department admissions for diverticulitis occur annually in the United States.[4]

Despite the clinical and economic importance of diverticular disease, its pathophysiology remains poorly understood.[2, 5] Contemporary data now associate the disease with microbiome alterations and chronic inflammation.[2, 5] Statins (HMG-CoA reductase inhibitors) are common prescription drugs primarily used to reduce low-density lipoprotein cholesterol levels to prevent cardiovascular disease.[6] In addition, statins exert pleiotropic anti-inflammatory effects,[7] paving the way for a possible role of these drugs to prevent diverticular disease.[8, 9]

To our knowledge, only three case-control studies have investigated this topic. Humes, *et al.* used the United Kingdom General Practice Research Datalink to identify 899 cases of perforated diverticular disease during 1990–2005, reporting a protective effect of statins (odds ratio [OR]: 0.44).[8] Two other case-control analyses failed to find such protective effects.[9, 10] In a Swedish population-based study, Sköldberg, *et al.* found an overall null results, but a protective effect for cases requiring surgery (OR: 0.70).[9] Similarly, O'Grady, *et al.* assessed 643 patients with diverticular disease presenting at Christchurch Hospital, New Zealand, and found no overall association, although an apparently protective effect was observed among those aged more than 65 years (OR: 0.47).[10] Importantly, none of the previous studies reporting on this topic adjusted for diet, physical activity, or alcohol consumption–three potentially important confounders–and only the study by Humes *et al.* adjusted for smoking.[8]

To further add to the evidence base and to correct for the previous shortcomings, we undertook a nationwide registry-based analysis of the effect of statins on the risk of diverticular disease.

MATERIALS AND METHODS

Setting, design, and data sources

The Danish national health service provides unrestricted access to tax-financed health care to all legal residents of Denmark, including partial reimbursement for prescription drugs.[11]

We performed a nested case-control study among participants of the 2010 or the 2013 Danish National Health Survey (DNHS) – a cross-sectional, nationwide health survey carried out regularly.[12] In 2010 and 2013, a representative sample of citizens aged 16 years or older residing in Denmark were asked to participate: 177,639 (60%) completed the self-administered questionnaire in 2010 and 183,372 (54%) in 2013. We restricted the study population to first-time respondents and to adults ≥18 years. The survey design has been described in detail elsewhere.[12]

We linked our study population to three additional data sources: The Danish National Patient Registry (DNPR),[13] the Danish National Health Service Prescription Database (DNHSPD),[14] and the Danish Cancer Registry (DCR).[15] This was possible by virtue of the unique, ten-digit personal identifier assigned to each resident at birth or upon immigration.[16] The DNHSPD contains detailed, nationwide data on all drug prescriptions redeemed in outpatient pharmacies since 2004. The DNPR contains records of all hospital inpatient department diagnoses since 1977 and outpatient and emergency department diagnoses since 1995. Diagnoses are coded according to the International Classification of Diseases (ICD). The DNPR also contains data on surgical procedures coded, since 1996, according to the Nordic Medico-Statistical Committee System (NOMESCO). The DCR has recorded all incident cancer diagnoses since 1943. Cancers are coded according to the ICD-10 (recoded from ICD-7 before

2004). These registries were used to identify cases and controls (DNPR), exposure (DNHSPD), covariates (DNPR, DNHSPD), and exclusion criteria (DNPR, DCR).

Cases

We identified cases, nested within the DNHS participants, as those with a first-time inpatient-, outpatient clinic, or emergency department diagnosis of colonic diverticular disease anytime between questionnaire completion and 31 December 2018. In Denmark, the vast majority of diverticular disease diagnoses is based on computed tomography scanning or colonoscopy performed in hospital settings. We excluded cases with a history of inflammatory bowel disease and colorectal cancer due to the increased colonoscopic surveillance associated with these conditions, as well as those with a history of active liver disease as it is a contraindication for statins. We searched for primary or secondary discharge diagnoses of these conditions recorded at any time before the date of diverticular disease (index date). Table S1 lists all diagnostic codes used to define the case definitions.

Controls

Applying a risk-set sampling strategy,[17] we selected 10 diverticular disease-free controls among DNHS respondents for each case, matched on sex, age, and year of survey. Controls were assigned the same index date as that of the matched case. We permitted individuals to be selected as controls more than once, and for controls to later become cases.[18] We applied the same exclusion criteria to controls as to cases.

Exposure definition

Based on virtually complete prescription records from Danish community pharmacies since 2005, we defined ever use as ≥1 filled statin prescription before the index date and never use as no filled statin prescription. Additionally, we altered the exposure definition according to various

criteria. First, statin exposure was quantified according to the cumulative duration (defined as the number of days between the first and the last prescription filling plus a 60-day grace period), cumulative dose (defined as the total amount in defined daily doses [DDD]), and intensity of use (defined as the cumulative duration divided by the cumulative dose). Second, we classified ever use as current use (latest prescription filling within 90 days before the index date) and former use (latest prescription filling more than 90 days before the index date). Third, because the overall statins class comprise drugs with distinct biochemical structures and pharmacokinetics, we categorized statins into lipophilic (simvastatin, lovastatin, fluvastatin, atorvastatin, cerivastatin) and hydrophilic (pravastatin, rosuvastatin) statins. Last, based on the first filled prescription, we categorized ever use as low intensity, moderate intensity, and high intensity use, according to recommendations from the American Heart Association.[19] This categorization is based on the presumed reduction in low-density lipoprotein cholesterol levels (<30%, 30–49%, and ≥50%, respectively) according to the prescribed statin class and daily dose.

Covariates

Based on all available records in the DNPR since 1977 and before the index date, we obtained data on the following hospital-based discharge diagnoses potentially associated with both statin use and diverticular disease: myocardial infarction, stroke, heart failure, diabetes, hypertension, atrial fibrillation, and chronic obstructive pulmonary disease (COPD). From the DNHSPD, we also obtained data on prescriptions other than statins filled within six months before the index date: non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, antiplatelets, angiotensin-converting enzyme/angiotensin 2 receptor inhibitors, beta-blockers, calcium channel blockers, diuretics, glucocorticoids, and opioids. These drugs were selected based on their presumed association with diverticular disease.[2] Finally, from the DNHS, we obtained information on lifestyle-related variables: diet (healthy, reasonably healthy, unhealthy [definitions below]), body mass index (underweight [<18.5], normal weight [18.5–<25], overweight [25–<30], obese [>30]),

smoking (never, current, former), alcohol intake (low risk consumption [≤7/14 drinks weekly, women/men], high risk consumption [>7/14 drinks weekly, women/men]),[20] leisure time physical activity (low, medium, high), education (none, student, short, medium, long, other), and occupation (student, early retirement, unemployed, employed, state pensioner).

The Dietary Quality Score, developed by the Research Centre for Prevention and Health, Denmark, was used as an aggregated dietary measure, categorizing respondents as "healthy" (high intake of fruit, vegetables, fish and low amounts of saturated fat), "reasonably healthy" (medium intake of fruit, vegetables, fish, and saturated fat), or "unhealthy" (low intake of fruit, vegetables, fish, and high amounts saturated fat).[21]

Statistical analyses

Main analyses

We characterized cases and controls according to sex, age, and the covariates described above. Using conditional logistic regression, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) associating diverticular disease with ever use of statins. By virtue of the risk-set sampling strategy, the estimated ORs resemble the incidence rate ratios that would have arisen from a cohort study.[17] By design, minimally-adjusted ORs were controlled for age, sex, and calendar time, while fully-adjusted models additionally included the remaining covariates. In all analyses, never users of statins served as the reference.

Additional analyses

We repeated the main analyses altering the exposure definition. First, we evaluated dose-response by performing the analyses according to the cumulative duration (0–1 year, 2–5 years, 6–9 years, and 10+ years) and cumulative dose (0–999 DDD, 1000–2999 DDD, and 3000+ DDD). As well, in analyses taking into account both the cumulative duration and dose, we arbitrarily classified users as low intensity, medium intensity, and high intensity users. Within

these categories, we repeated the analysis for short-term users (<5 years) and long-term users (≥5 years). Second, we repeated the analysis for current and former users. Third, we assessed the association separately for lipophilic and hydrophilic statins. Lastly, we compared statin intensities head-to-head using the intensity classification recommended by the American Heart Association.[19] In this analysis, low intensity statin use served as the reference.

We stratified the main analyses by sex and age group (18–60 years, 61+ years). Then, because statins may be associated with certain degrees of diverticular disease severity and not others, we repeated the main analysis classifying cases on a mutually exclusive basis in order of severity: 1) diverticular disease surgically treated (including laparoscopic lavage), 2) diverticular disease conservatively treated during an acute admission, and 3) other cases of diverticular disease treated in the outpatient department. Table S1 specifies these definitions. Finally, we estimated the absolute incidence rates of diverticular disease in the underlying DNHS cohort according to statin exposure. To do so, we calculated and used the event rate for statin never users as the reference and multiplied this rate with the ORs (as this measure resemble the incidence rate ratio) obtained for the different statin exposure definitions.

Sensitivity analyses

We performed four sensitivity analyses. First, to examine the role of diagnostic bias present in our data, we repeated the main analysis restricting to those cases and controls who had a colonoscopy performed before the index date. It seems plausible that statin users may have a closer relation to the health care system and a larger degree of adherence to colonoscopic screening for colorectal cancer compared with non-users. Consequently, statin users may be more likely to receive a diagnosis of diverticular disease, particularly in case of asymptomatic disease. Thus, if diagnostic bias is present, the results of the main analysis would be biased upwards. Restricting the analysis to patients with a previously performed colonoscopy would diminish or remove this bias. For this analysis, we dissolved the matching and additionally

adjusted for sex, age, and year of survey. Second, in an additional analysis of the potential diagnostic bias present in these data, we examined the association between ever use of glaucoma drugs and never use of glaucoma drugs. In this analysis, glaucoma drugs served as a negative control exposure (*i.e.*, no presumed effect on diverticular disease). Similar to the main analysis comparing ever users with never users of statins, if diagnostic bias is present, the observed OR in the analysis would be expected to be biased upwards. Third, to examine the impact of early nonadherence, we altered our main exposure definition to ≥2 filled prescriptions and the reference to 0–1 filled prescriptions for a statin. Fourth, to examine the potential for reverse causality, we performed an analysis ignoring prescriptions filled within one year before the index date.

Diagnosis codes are provided in Table S1, and a study flowchart is provided in Figure S1. We used SAS statistical software package, v. 9.2 (SAS Institute, Cary, NC) to conduct all analyses. The study was approved by the Danish Data Protection Agency. Registry-based studies do not need ethical board approval in Denmark.[22]

RESULTS

Patient characteristics

The analysis comprised 8,809 incident cases with diverticular disease and 88,090 matched controls (Table 1). Women constituted slightly more than half of the study population (54%); the median age at diagnosis/index date was 64 years. Compared with controls, cases had a higher burden of hospital-diagnosed morbidities, including hypertension (28% *vs*. 19%), atrial fibrillation (10% *vs.* 7%), and COPD (8% *vs.* 5%), and more frequently used cardiovascular medication other than statins. Accordingly, cases were slightly more frequently classified as unhealthy (13% *vs.* 11%), obese (20% *vs.* 15%), and smoker (22% *vs.* 20%). The degree of missingness for lifestyle-related variables did not seem dependent on case status.

Main analyses

A total of 3,856 (44%) cases with diverticular disease and 31,851 (36%) controls were identified as ever users of statins, yielding a minimally-adjusted OR of 1.42 (95% CI: 1.36–1.49) (Table 2). In fully-adjusted analyses, adjustment for the pre-specified covariates indicated positive confounding (fully-adjusted OR: 1.19 [95% CI: 1.12–1.27]) but the association persisted. Adjustment for hospital-based morbidities and medication use drove the change in effect estimates (Table S2).

Additional analyses

In dose-response analyses, associations generally persisted irrespective of cumulative duration, cumulative dose, and intensity (Table 2). For example, among short-term users (<5 years), the fully-adjusted OR was 1.18 (95% CI: 1.04–1.35) for low intensity users, 1.34 (95% CI: 1.18–1.52) for medium intensity users, and 1.13 (95% CI: 1.01–1.26) for high intensity users. Similarly, among long-term users (≥5 years), the respective ORs were 1.25 (95% CI: 1.13–1.38), 1.13 (95% CI: 1.02–1.25), and 1.11 (95% CI: 0.98–1.24). Analyses of former and current use yielded comparable results to those from the main analysis. Results did not appear contingent on drug lipophilicity, although this analysis was hampered by low users of hydrophilic statins. When using the American Heart Association definitions to compare low intensity users with moderate intensity (fully-adjusted OR: 1.01 [95% CI: 0.87–1.16]) and high intensity users (fully-adjusted OR: 1.02 [95% CI: 0.82–1.27]), associations were close to null.

The association was virtually identical for men and women and robust within age groups (Table S3). Among the discrete case definitions, we identified 486 (6%) cases with diverticular disease surgically treated, 1,693 (19%) cases with diverticular disease conservatively treated, and 6,630 (75%) other cases of diverticular disease (Table 3). Within these definitions, the associations were generally robust, although slightly elevated among cases conservatively treated (fully-adjusted OR: 1.35 [95% CI: 1.16-1.58]).

The absolute incidence rates of diverticular disease associated with statin exposure are presented in Table 5.

Sensitivity analyses

When restricting to the 1,160 cases and 6,094 controls with a previous colonoscopy, the association was virtually null (fully-adjusted OR: 1.01 [95% CI: 0.85-1.20]) (Table 4). Examining the association with diverticular disease comparing ever use with never use of glaucoma drugs, the results resembled that of the main analysis with statins, although the association was less pronounced (fully-adjusted OR: 1.11 [95% CI: 0.98-1.25]) (Table S4). Finally, in analyses altering the exposure definition to ≥2 filled prescriptions and the reference to 0–1 filled prescriptions for a statin (fully-adjusted OR: 1.15 [95% CI: 1.08-1.23]), and in analyses ignoring prescriptions filled within one year before the index date (fully-adjusted OR: 1.17 [95% CI: 1.09-1.24]), associations were robust with the main analyses (Table S5–S6).

DISCUSSION

Main findings

In this large case-control analysis nested within a nationwide health survey, the higher observed risk of diverticular disease associated with statin use could be explained by diagnostic bias. We note several points that must be considered when interpreting our results.

First, we found a near-null association when restricting to those cases and controls who had a colonoscopy performed before the index date. This suggests that diagnostic bias, arising from ever users of statin being more likely than never users to utilize healthcare services, including colonoscopies in relation to colorectal cancer screening or for other indications, could explain the observed association. In line with this, the finding of a slight association with glaucoma drugs, a presumed negative exposure, is also indicative of the presence of this source of bias in these data, although the association was less pronounced.

Second, we note a lack of a dose-response relation associated with statins: ORs in the short-term (*i.e.*, 0–1 years) and in the long-term (*i.e.*, 10+ years) indicated consistently elevated risks of around 20%. In analyses taking into account both duration and intensity, the elevated risk appeared independent of both duration and intensity. As well, when comparing different statin intensities head-to-head, associations were close to null. The lack of a clear dose-response pattern speaks against causality.

Third, we must also note that considering the pleiotropic inflammatory effects of statins,[7] in conjunction with previous, albeit limited, research,[8] we hypothesized that statins be associated with beneficial effects on risk of diverticular disease. Our findings certainly did not suggest such an effect. Taking these points together, any effect of statins on diverticular disease, if present, is probably small.

Comparison with previous findings

Diverticular disease is a complex entity comprised of a range of associated conditions.[2] For example, our overall definition of diverticular disease comprised both uncomplicated cases as well as complicated cases that could lead to colonic perforation or abscess. Previous studies examining the potential for statins to impact the occurrence of diverticular disease have used varying definitions.[8-10]

Our results agree largely with those reported by Sköldberg, *et al.*[9] and O'Grady, *et al.*[10] that both estimated near-null associations between statin use and diverticular disease. Despite the null-association with overall diverticular disease, Sköldberg, *et al.* found a protective effect for cases requiring surgery (OR: 0.70 [95% CI: 0.55–0.89]).[9] These authors also performed a sensitivity analysis with users of glaucoma drugs as references, instead of never statin users, and found associations close to unity for all types of diverticular disease. In contrast with these findings, Humes, *et al.* showed an approximately 50% reduced risk of perforated colonic diverticular disease in current users of statins, although a null association was observed for ever

users.[8] This analysis, however, was based on only seven current users among cases and 142 users among controls, which may partly explain the inconsistencies in the observed effect estimates. Thus, the divergent results observed in previous studies and those from the current study leaves little indication that statins impact the risk of diverticular disease to a great extent.

Strengths and limitations

Strengths of the current study include the uniformly organized health care system, including individual-level data on hospital-based diagnoses and filled prescriptions.[11] The population-based registries used in this study are updated continuously with prospectively collected data. Our study was nested within a nationwide, representative health survey, which provided us with detailed data on important lifestyle-related factors such as diet, body mass index, smoking, and alcohol consumption.

Given the registry-based outcome data, our effect estimates depend on the validity of the diagnostic coding. The codes used to define diverticular disease in the present study has been reported to be high with a positive predictive value of 98%, although codes used to define subclassifications of diverticular disease were somewhat lower.[23] The ICD-10 coding of diverticular disease in the DNPR did not allow us to incorporate the clinical terminology commonly used to subgroup the disease into complicated and uncomplicated cases. Our attempt to categorize cases based on presence or absence of a surgery code is thus merely a proxy for disease severity.

We must also note the potential for unmeasured or residual confounding given the observational nature of our study. However, we had access to an extensive web of covariates, including data on lifestyle-related factors that normally are absent in registry-based studies. Indeed, our findings suggest a large degree of positive confounding. To this end, it is also important to note the absence of a “healthy user effect” in our study population, *i.e.*, statin users are not healthier than no-users, which has been identified in other settings.[24] Lastly, it is

possible that some statin users were erroneously categorized as never users if statin therapy was initiated (and terminated) before the commencement of the DNHSPD in 2004. This type of misclassification could have moved the effects estimates towards unity.

Our study did not support a protective nor harmful effect of statins on the risk of diverticular disease. The observed association of a higher risk associated with statins could be explained by diagnostic bias.

Conflicts of interest disclosure statement

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.

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.

Ethical approval statement

The study was approved by the Danish Data Protection Agency. Registry-based studies do not need ethical board approval in Denmark.

Patient consent form

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

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Table 1. Characteristics (N, %) of cases with diverticular disease and risk-set matched controls

	Cases (N=8,809)	Controls (N=88,090)
Female sex	4,725 (53.6)	47,250 (53.6)
Median age (IQR)	64 (57-72)	64 (57-72)
Morbidities		
Myocardial infarction	306 (3.5)	2,566 (2.9)
Stroke	369 (4.2)	3,427 (3.9)
Heart failure	361 (4.1)	2,603 (3.0)
Diabetes	956 (10.9)	8,090 (9.2)
Hypertension	2,473 (28.1)	16,268 (18.5)
Atrial fibrillation	877 (10.0)	5,980 (6.8)
COPD	683 (7.8)	4,206 (4.8)
Medication use		
NSAIDs	1,432 (16.3)	10,828 (12.3)
Paracetamol	2,500 (28.4)	17,542 (19.9)
Antiplatelets	2,022 (23.0)	16,287 (18.5)
ACE/angiotensin 2 receptor inhibitors	1,207 (13.7)	10,415 (11.8)
Beta-blockers	1,791 (20.3)	13,881 (15.8)
Calcium channel blockers	1,678 (19.0)	14,633 (16.6)
Diuretics	1,961 (22.3)	15,489 (17.6)
Glucocorticoids	492 (5.6)	3,171 (3.6)
Opioids	1,253 (14.2)	7,716 (8.8)
Diet		
Healthy	1,877 (21.3)	20,712 (23.5)
Reasonably healthy	5,297 (60.1)	52,945 (60.1)
Unhealthy	1,141 (13.0)	9,715 (11.0)
Missing	494 (5.6)	4,718 (5.4)
Body mass index		
<18.5	81 (0.9)	1,214 (1.4)
18.5–<25	3,028 (34.4)	37,004 (42.0)
25–<30	3,583 (40.7)	33,594 (38.1)
>30	1,798 (20.4)	13,124 (14.9)
Missing	319 (3.6)	3,154 (3.6)
Smoking		
Never	3,005 (34.1)	35,002 (39.7)
Current	1,961 (22.3)	17,250 (19.6)
Former	3,597 (40.8)	33,292 (37.8)
Missing	246 (2.8)	2,546 (2.9)
Alcohol consumption		
Low risk	6,161 (69.9)	62,441 (70.9)
High risk	2,053 (23.3)	20,081 (22.8)
Missing	595 (6.8)	5,568 (6.3)
Physical activity in leisure time		
Low	1,451 (16.5)	12,426 (14.1)
Medium	6,891 (78.2)	70,898 (80.5)
High	84 (1.0)	1,153 (1.3)
Missing	383 (4.3)	3,613 (4.1)
Education		
None	1,559 (17.7)	13,709 (15.6)
Student	24 (0.3)	265 (0.3)
Short	3,152 (35.8)	30,915 (35.1)
Medium	2,362 (26.8)	24,452 (27.8)
Long	522 (5.9)	7,076 (8.0)
Other	432 (4.9)	4,429 (5.0)
Missing	758 (8.6)	7,244 (8.2)

Occupation		
Student	23 (0.3)	325 (0.4)
Early retirement	479 (5.4)	3,686 (4.2)
Unemployed	275 (3.1)	2,550 (2.9)
Employed	2,958 (33.6)	31,511 (35.8)
State pensioner	4,903 (55.7)	48,446 (55.0)
Missing	171 (1.9)	1,572 (1.8)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease

Table 2. Use of statins and risk of diverticular disease.

Statin exposure	Cases (N=8,809)	Controls (N=88,090)	Odds ratio (95% CI)	
			Adjusted*	Fully-adjusted†
Never use	4,953 (56.2)	56,239 (63.8)	1.00 (ref)	1.00 (ref)
Ever use	3,856 (43.8)	31,851 (36.2)	1.42 (1.36-1.49)	1.19 (1.12-1.27)
Cumulative duration				
0–1 year	507 (5.8)	4,083 (4.6)	1.45 (1.31-1.59)	1.31 (1.16-1.47)
2–5 years	981 (11.1)	8,364 (9.5)	1.37 (1.27-1.47)	1.16 (1.06-1.27)
6–9 years	1,586 (18.0)	13,212 (15.0)	1.41 (1.33-1.51)	1.15 (1.06-1.25)
10+ years	782 (8.9)	6,192 (7.0)	1.52 (1.39-1.66)	1.21 (1.08-1.35)
Cumulative dose				
0–999 DDD	1,103 (12.5)	9,056 (10.3)	1.42 (1.32-1.52)	1.24 (1.14-1.35)
1000–2999 DDD	1,490 (16.9)	12,415 (14.1)	1.41 (1.33-1.51)	1.20 (1.10-1.30)
3000+ DDD	1,263 (14.3)	10,380 (11.8)	1.44 (1.35-1.55)	1.10 (1.00-1.21)
Intensity and duration				
Short-term use (<5 years)				
Low intensity	424 (4.8)	3,677 (4.2)	1.35 (1.21-1.50)	1.18 (1.04-1.35)
Medium intensity	429 (4.9)	3,280 (3.7)	1.52 (1.37-1.69)	1.34 (1.18-1.52)
High intensity	635 (7.2)	5,490 (6.2)	1.35 (1.24-1.47)	1.13 (1.01-1.26)
Long-term use (≥5 years)				
Low intensity	859 (9.8)	6,941 (7.9)	1.47 (1.36-1.59)	1.25 (1.13-1.38)
Medium intensity	883 (10.0)	7,311 (8.3)	1.43 (1.33-1.55)	1.13 (1.02-1.25)
High intensity	626 (7.1)	5,152 (5.8)	1.44 (1.31-1.57)	1.11 (0.98-1.24)
Current use	2,375 (27.0)	20,114 (22.8)	1.39 (1.32-1.47)	1.13 (1.05-1.22)
Former use	1,481 (16.8)	11,737 (13.3)	1.48 (1.39-1.58)	1.26 (1.17-1.37)
Lipophilicity				
Lipophilic statins	3,807 (43.2)	31,518 (35.8)	1.41 (1.35-1.48)	1.18 (1.11-1.26)
Hydrophilic statins	539 (6.1)	3,907 (4.4)	1.41 (1.28-1.55)	1.10 (0.98-1.23)
Intensity according to the American Heart Association				
Low intensity	320 (8.3)	2,772 (8.7)	1.00 (ref)	1.00 (ref)
Moderate intensity	3,317 (86.0)	27,312 (85.7)	1.05 (0.93-1.18)	1.01 (0.87-1.16)
High intensity	219 (5.7)	1,767 (5.4)	1.06 (0.89-1.28)	1.02 (0.82-1.27)

Abbreviation: CI, confidence interval; DDD, defined daily dose.

*****Adjusted for sex, age, and year of survey by design.

†Additionally adjusted for myocardial infarction, stroke, heart failure, diabetes, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, use of non-steroidal anti-inflammatory drugs, paracetamol, antiplatelets, angiotensin-converting enzyme/angiotensin 2 receptor inhibitors, beta-blockers, calcium channel blockers, diuretics, glucocorticoids, opioids, diet, body mass index, smoking, alcohol intake, physical activity, education, and occupation.

Table 3. Use of statins (never use is the reference) and risk of diverticular disease surgically treated, diverticular disease conservatively treated, and other cases of diverticular disease.

Diverticular disease	Exposure, cases	Exposure, controls	Odds ratio (95% CI)	
			Adjusted*	Fully-adjusted†
Diverticular disease surgically treated, N = 486	206 (42.4)	1,864 (38.4)	1.20 (0.98-1.46)	1.19 (0.91-1.56)
Diverticular disease conservatively treated, N = 1,693	680 (40.2)	5,180 (30.6)	1.64 (1.47-1.84)	1.35 (1.16-1.58)
Other cases of diverticular disease, N = 6,630	2,970 (44.8)	24,807 (37.4)	1.40 (1.33-1.47)	1.16 (1.08-1.25)

Abbreviation: CI, confidence interval.

*****Adjusted for sex, age, and year of survey by design.

†Additionally adjusted for myocardial infarction, stroke, heart failure, diabetes, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, use of non-steroidal anti-inflammatory drugs, paracetamol, antiplatelets, angiotensin-converting enzyme/angiotensin 2 receptor inhibitors, beta-blockers, calcium channel blockers, diuretics, glucocorticoids, opioids, diet, body mass index, smoking, alcohol intake, physical activity, education, and occupation.

Table 4. Use of statins (never use is the reference) and risk of diverticular restricted to cases and controls with a previous colonoscopy performed. Matching is dissolved.

Statin exposure	Cases (N=1160)	Controls (N=6094)	Odds ratio (95% CI)	
			Unadjusted*	Fully-adjusted†
Never use	588 (50.7)	3,245 (53.2)	1.00 (ref)	1.00 (ref)
Ever use	573 (49.4)	2,852 (46.8)	1.11 (0.98-1.26)	1.01 (0.85-1.20)

Abbreviation: CI, confidence interval.

*****Adjusted for sex, age, and year of survey.

†Additionally adjusted for myocardial infarction, stroke, heart failure, diabetes, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, use of non-steroidal anti-inflammatory drugs, paracetamol, antiplatelets, angiotensin-converting enzyme/angiotensin 2 receptor inhibitors, beta-blockers, calcium channel blockers, diuretics, glucocorticoids, opioids, diet, body mass index, smoking, alcohol intake, physical activity, education, and occupation.

Table 5. Absolute incidence rates of diverticular disease according to statin exposure.

Statin exposure	**Incidence rate of diverticular disease per 1,000 person-years in the Danish National Health Survey**
Never use	3.0
Ever use	3.5
Cumulative duration	
0–1 year	3.9
2–5 years	3.5
6–9 years	3.4
10+ years	3.6
Cumulative dose	
0–999 DDD	3.7
1000–2999 DDD	3.6
3000+ DDD	3.3
Intensity and duration	
Short-term use (<5 years)	
Low intensity	3.5
Medium intensity	4.0
High intensity	3.4
Long-term use (≥5 years)	
Low intensity	3.7
Medium intensity	3.4
High intensity	3.3
Current use	3.4
Former use	3.7
Lipophilicity	
Lipophilic statins	3.5
Hydrophilic statins	3.3
Intensity according to the American Heart Association	
Low intensity	3.0
Moderate intensity	3.0
High intensity	3.0