A population-based case–control study on statin exposure and risk of acute diverticular disease

FILIP SKÖLDBERG1, TOBIAS SVENSSON2, OLA OŁEN2,3,4, FREDRIK HJERN5, PETER T. SCHMIDT6 & RICKARD LJUNG7

1Department of Surgical Sciences, Uppsala University, Uppsala, Sweden, 2Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, 3Sachs’ Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden, 4Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden, 5Division of Surgery, Department of Clinical Sciences, Danderyd University Hospital, Stockholm, Sweden, 6Unit of Gastroenterology and Hepatology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, and 7Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

ABSTRACT
Objective: A reduced risk of perforated diverticular disease among individuals with current statin exposure has been reported. The aim of the present study was to investigate whether statins reduce the risk of acute diverticular disease.

Material and methods: A nation-wide population-based case–control study was performed, including 13,127 cases hospitalised during 2006–2010 with a first-time diagnosis of colonic diverticular disease, and 128,442 control subjects (matched for sex, age, county of residence and calendar year). Emergency surgery, assumed to be a proxy for complicated diverticulitis, was performed on 906 of the cases during the index admission, with 8,818 matched controls. Statin exposure was classified as “current” or “former” if a statin prescription was last dispensed ≤125 days or >125 days before index date, respectively. The association between statin exposure and acute diverticular disease was investigated by conditional logistic regression, including models adjusting for country of birth, educational level, marital status, comorbidities, nonsteroidal anti-inflammatory drug/steroid exposure and healthcare utilisation.

Results: A total of 1959 cases (14.9%) and 16,456 controls (12.8%) were current statin users (crude OR 1.23 [95% CI 1.17–1.30]; fully adjusted OR 1.00 [0.94–1.06]). One hundred and thirty-two of the cases subjected to surgery (14.6%), and 1441 of the corresponding controls (16.3%) were current statin users (crude OR 0.89 [95% CI 0.73–1.08]; fully adjusted OR 0.70 [0.55–0.89]).

Conclusions: The results do not indicate that statins affect the development of symptomatic diverticular disease in general. However, current statin use was associated with a reduced risk of emergency surgery for diverticular disease.

ARTICLE HISTORY
Received 30 May 2015
Revised 26 July 2015
Accepted 3 August 2015
Published online 4 September 2015

KEYWORDS
Case–control studies, diverticulitis, hydroxymethylglutaryl-CoA reductase inhibitors, pharmacoepidemiology

Introduction
In western societies, the presence of colonic diverticula (diverticulosis) becomes a common condition with increasing age, affecting less than 10% of individuals aged under 40, and 50–70% of those aged over 80 years [1]. Whereas diverticulosis itself is generally asymptomatic, diverticula may become inflamed, a condition termed diverticulitis. It has been estimated that some 10–15% of patients with diverticula develop diverticulitis [1], but recent studies indicate that the true incidence is considerably lower [2]. This condition can range from “uncomplicated” diverticulitis, a usually self-limiting condition with pericolic inflammation, to “complicated” diverticulitis with the development of abscess, fistula or peritonitis due to diverticular perforation, which may require surgical intervention [3]. Surgical options include a diverting stoma, Hartmann’s procedure, resection with primary anastomosis, and (laparoscopic) lavage with drainage of the abdominal cavity [4]. A Danish study indicates that the diagnostic coding for colonic diverticular disease in the International Classification of Diseases, 10th Revision (ICD-10), does not allow reliable identification of cases with abscess or perforation [5]. However, emergency surgery is usually reserved for cases of “complicated” diverticulitis [3], and has been used for distinguishing these from those of “uncomplicated” disease [6].

The pathogenesis of diverticular disease is not fully understood. Recent studies indicate that genetic predisposition is of importance [7,8]. Several lifestyle-related
risk factors have also been implicated, including diet, obesity and physical inactivity and smoking [9–11]. Users of nonsteroidal anti-inflammatory drugs (NSAIDs) are at increased risk of developing diverticulitis, and use of systemic glucocorticoids is associated with an increased risk of perforated diverticulitis [12]. In a case–control study using data from the UK General Practice Research Database, an apparent protective effect of statins (HMG-CoA reductase inhibitors) on the risk of perforated colonic diverticular disease was found [13]. An anti-inflammatory effect of statins in the colon is suggested by the finding that the HMG-CoA reductase inhibitor fluvastatin reduces the severity of colitis in dextran sodium sulphate-treated rodents (a model for ulcerative colitis) [14,15]. Increased knowledge of the impact of different drugs on diverticular disease may be of value in reducing patients’ risk for incident or recurrent symptomatic diverticular disease, as well as provide clues to the pathogenesis.

The aim of the present study was to investigate if statin use affects the risk for acute diverticular disease requiring hospitalisation, and the possible impact of statin use on the risk of acute diverticular disease requiring emergency surgery (the latter being assumed to be a proxy for “complicated” disease).

Methods

Study design

The study was performed as a nation-wide population-based case–control study using cross-linked data from national Swedish registers. Residents of Sweden aged 25–89 years during the period between 2006 and 2010 constituted the source population. Individuals with a first-time diagnosis of diverticular disease of the colon during the study period were identified from the National Patient Register, and control subjects randomly selected from the Swedish Register of the Total Population. It was assumed that a possible protective effect of statins would be present for acute diverticulitis, rather than diverticular bleeding or mere diverticulosis. Thus, the outcome studied was restricted to cases who were subject to non-elective hospitalisation in a surgical unit with a first-time diagnosis of diverticular disease, excluding those with a diagnostic coding for a gastrointestinal haemorrhage or procedures rarely performed during an attack of acute diverticulitis. Data on drug exposures and previous comorbidities were retrieved from the Prescribed Drug Register and the National Patient Register, respectively. The Swedish Register of the Total Population was used to collect data on country of birth and marital status. Individual records of highest formal educational level were obtained from the Swedish National Education Register. Information on any diagnosis of malignancy for all subjects was retrieved from the Swedish Cancer Register. Data from different registers were linked using the personal identity number assigned to every resident of Sweden [16].

Registers

The Swedish healthcare system is tax-funded and offers universal access. The National Patient Register, founded in 1964, contains information on diagnoses and surgical procedures recorded at public and private specialist healthcare providers. The coverage is complete for inpatient care since 1987 and outpatient specialist care since 2001. For inpatients, admissions are recorded as acute or planned [17].

The Swedish Register of the Total Population contains individual characteristics on all Swedish residents since 1968, including age, sex, country of birth, marital status and place of residence as well as dates of birth, death and emigration status [18].

Since 1 July 2005, all prescribed medications dispensed at pharmacies in Sweden are recorded in the Prescribed Drug Register [19]. The record includes Anatomical Therapeutic Chemical (ATC) classification codes [20], amounts of the prescribed drugs and date of dispensing.

The Causes of Death Register contains information on all deceased Swedish residents since 1952 [21].

The Swedish Cancer Register, founded in 1958, contains records on all newly detected primary malignancies, whether diagnosed clinically, by histological investigations or at autopsy. Data include site of tumour, histological type and basis of diagnosis. Reporting is compulsory for all healthcare providers, and in a comparison with the National Patient Register in 1998, coverage was estimated to >96% [22].

The National Education Register was established by Statistics Sweden in 1985 and is annually updated with information on the highest formal education attained by each individual, from elementary to postgraduate level [23].

Case and control identification

Cases were persons with a first-time diagnosis of diverticular disease of the colon recorded in the National Patient Register 1 January 2006–30 June 2010, with no prior record of colonic diverticular disease since 1964. Cases were further restricted to patients with a first-time primary diagnosis of colonic diverticular disease or a primary diagnosis of peritonitis with a secondary diagnosis of diverticular disease, subjected
to acute admission for inpatient care in surgical, emergency-care or gastrointestinal units. Any patients with a concomitant diagnosis code for rectal/gastrointestinal bleeding or surgical procedure code for flexible endoscopy of the lower gastrointestinal tract or stoma revision/reversal, procedures infrequently performed in the context of acute diverticulitis, were excluded. The day of the first admission for diverticular disease was defined as the index date.

To identify a subgroup of cases that could be assumed to have complicated diverticular disease, subjects who were subjected to one of the following surgical procedures during the index hospitalisation were identified: laparotomy or laparoscopy with draining or lavage, intestinal resections, open or laparoscopic formation of a loop ileostomy, enterostomy, caecostomy, transversostomy, sigmoidostomy or other colostomy [24].

For each of the selected cases, up to 10 control subjects were randomly sampled from the Swedish Register of the Total Population and assigned the same index date as their respective case, matching for sex, age, county of residence and calendar year. Matching data were retrieved from the beginning of each calendar year, and only individuals not diagnosed with diverticular disease of the colon before or throughout the year, and only individuals not diagnosed with diverticular disease of the colon before or throughout the calendar year of the index date were eligible as controls. Control subjects who were deceased before their respective index dates were discarded from the sample.

Any case or control with a previous diagnosis of colorectal cancer reported to the Swedish Cancer Register was excluded. To reduce any misclassification due to colorectal and other malignancies initially being misdiagnosed as diverticulitis, subjects with a diagnosis of a malignancy within 180 days after the index date as reported to the Swedish Cancer Register were also excluded. Each group of case and controls was assigned a unique identification number. The diagnostic and procedural codes used are listed in Appendix 1.

**Statin exposure**

Data on dispensing of prescribed statins [20] prior to index date were retrieved from the Prescribed Drug Register. ATC codes used are listed in Appendix 1. In Sweden, drugs for long-term use are normally prescribed for three-month periods of use, and package sizes are often at 98–100 units. It was assumed that prescriptions would usually cover 100 days of drug use, and with an added 25-day margin, current drug users were assumed to have had a drug dispensed within 125 days. Drug exposure was thus defined according to the time interval between the last date of dispensation and the index date, as follows: “current use” (1–125 days), “former use” (>125 days before the index date) days and “non-use” (no recorded drug dispensing since start of the register in 1 July 2005). Drugs dispensed on or after the index date were not considered.

**Control exposures**

In separate analyses, statin exposure was substituted with exposure for anti-glaucoma preparations and miotics or vitamin B12 (Appendix 1), with “current use” and “former use” defined as above, to serve as negative control exposures [25].

**Covariates**

In *a priori* discussions, we identified potential confounders that were assumed to be associated with statin exposure and potentially associated with the outcome, without being probable intermediates in the causal pathway. To control for comorbidities that may be associated with statin use and admission for acute diverticular disease, data were retrieved from the National Patient Register, Prescribed Drug Register and the Swedish Cancer Register. We adjusted for a history of diabetes mellitus, obesity, alcohol abuse, ischemic heart disease, stroke, chronic obstructive pulmonary disease, peripheral vascular disease renal disease and non-colorectal malignancy, excluding non-melanoma skin cancer (any malignant tumour reported to the Swedish Cancer Register prior to the eligible study subjects before the index date). The diagnostic and ATC codes used are listed in Appendix 1.

To control for possible socioeconomic confounding, data on country of birth (categorised as Sweden, other Nordic countries, non-Nordic EU-27 member countries and “other”), highest attained level of education (categorised as elementary school, secondary school, university and one category for missing data) and marital status (categorised as married or not married) were obtained from the Register of the Total Population and the National Education Register.

Exposures to systemic glucocorticoids and non-steroidal anti-inflammatory drugs recorded in the Prescribed Drug Register (Appendix 1), defined as for statin use (see above) were also adjusted for.

Furthermore, the number of hospitalisations within three years before the index date (categorised as 0, 1–3, 4–6, 7–9 and ≥10) and the number of out-patient specialist consultations within one year before the index date (categorised as 0, 1, 2, 3, 4 and ≥5), as reported to the National Patient Register, were also included in the final regression model as measures of healthcare utilisation.
**Immeasurable time**

For each individual, the number of days spent in hospital (for any reason) during the period 1–125 days before index date was calculated from on admission and release dates of in-patient records in the National Patient Register.

**Statistical analysis**

The association between statin use and acute diverticular disease was estimated by conditional logistic regression, conditioned on matched case–control sets, using the Stata version 12 software (StataCorp, College Station, TX). Adjustments were made in four models (with exposures defined as stated above): (1) A crude model with statin exposures only and no covariates. (2) A model adjusted for country of birth, educational level and marital status. (3) A model additionally adjusted for previous comorbidities and use of systemic steroids and prescribed NSAIDs. (4) A final model also adjusted for healthcare utilisation.

**Ethics**

The study was approved by the Regional Ethical Review Board in Stockholm (Dnr 2010/1111-32/2 and 2011/1317-32).

**Results**

**Study participants**

A total of 13,127 eligible cases were identified, of which 906 were subjected to any of the surgical procedures specified above, during the index hospitalisation. There were 128,442 control subjects included in the study, 8818 of whom were matched to the operated cases. The distribution of exposure variables in cases and controls is summarised in Table I. In the full study group, the observed frequency of both current and former statin exposure was more frequent among cases than controls, whereas among the operated cases current statin exposure was slightly less common than in their matched controls. The surgically treated cases were typically somewhat older than the complete group of cases (median age 61 and 67 years, respectively). Cases were predominantly female, but only slightly so in the operated group. A non-Nordic country of birth was somewhat more common among the controls. All comorbidities included were more frequent among cases, and notably 21.0% of the operated cases had a previous diagnosis of non-colorectal cancer. The observed frequencies of steroid and NSAID use were also higher among cases than controls, as was the degree of healthcare utilisation.

**Statin use and acute diverticular disease**

As shown in Table II, current statin use was associated with an increased risk of emergency hospitalisation for diverticular disease in the crude model (1.23, 95% CI 1.17–1.30). In the second model (adjusting for country of birth, educational level and marital status), the OR for current statin use was 1.22 (95% CI 1.16–1.29). In the third model (also adjusting for comorbidities, steroid use and NSAID use), the OR for current statin use was 1.02 (95% CI 0.96–1.09), whereas in the fully adjusted model (also adjusting for healthcare utilisation) it was 1.00 (95% CI 0.94–1.06). Former statin use was associated with an increased risk of hospitalisation for diverticular disease, also in the fully adjusted model (OR 1.14 [95% 1.04–1.25]).

**Statin use and acute diverticular disease requiring surgical treatment**

As described above, the subgroup of patients with acute diverticular disease treated by surgery was identified and analysed separately, in comparison to their respective controls. The results are shown in Table III. In the crude model, we found an OR for current statin use of 0.89 (95% CI 0.73–1.08), in the second model an OR of 0.87 (95% CI 0.71–1.06), in the third model an OR of 0.69 (95% CI 0.54–0.88) and in the fully adjusted model an OR of 0.70 (95% CI 0.55–0.89).

**Negative control exposures**

When replacing statin exposure with exposure for anti-glaucoma preparations and miotics or vitamin B12, we did not find an association in the fully adjusted model between “current use” and neither acute diverticular disease (anti-glaucoma preparations and miotics OR 0.93 [95% CI 0.83–1.03], vitamin B12 OR 0.99 [95% CI 0.91–1.08]), nor acute diverticular disease treated surgically (anti-glaucoma preparations and miotics OR 1.03 [95% CI 0.72–1.48], vitamin B12 OR 1.24 [95% CI 0.93–1.65]).

**Immeasurable time**

In the full group of 13,127 cases, 12.5% had been hospitalised during the period 1–125 days before index date (mean in-hospital time 1.2 days, 95th percentile 7 days). Among the corresponding 128,442 controls, 4.8% had been hospitalised during the same period (mean in-hospital time 0.4 days, 95th percentile 0 days). In the
| Characteristic                          | All cases and corresponding controls | Operated cases and corresponding controls |
|----------------------------------------|--------------------------------------|------------------------------------------|
|                                        | (n = 13,127)                         | (n = 906)                                |
|                                        | (n = 128,442)                        | (n = 8818)                               |
| Statin use                             |                                      |                                         |
| None                                   | 10,546 (80.3%)                       | 720 (79.5%)                             |
| Current (1–125 d)                      | 1959 (14.9%)                         | 132 (14.6%)                             |
| Former (>125 d)                        | 622 (4.7%)                           | 54 (6.0%)                               |
| Age group (years)                      |                                      |                                         |
| 25–29                                  | 104 (0.8%)                           | 8 (0.9%)                                |
| 30–34                                  | 261 (2.0%)                           | 12 (1.3%)                               |
| 35–39                                  | 566 (4.3%)                           | 21 (2.3%)                               |
| 40–44                                  | 954 (7.3%)                           | 42 (4.6%)                               |
| 45–49                                  | 1181 (9.0%)                          | 54 (6.0%)                               |
| 50–54                                  | 1375 (10.5%)                         | 106 (11.7%)                             |
| 55–59                                  | 1605 (12.2%)                         | 115 (12.7%)                             |
| 60–64                                  | 1851 (14.1%)                         | 125 (13.8%)                             |
| 65–69                                  | 1413 (10.8%)                         | 106 (11.7%)                             |
| 70–74                                  | 1195 (9.1%)                          | 1117 (12.7%)                            |
| 75–79                                  | 1066 (8.1%)                          | 1195 (13.6%)                            |
| 80–84                                  | 918 (7.0%)                           | 955 (10.8%)                             |
| 85–89                                  | 638 (4.9%)                           | 618 (7.0%)                              |
| Sex                                    |                                      |                                         |
| Male                                   | 5382 (41.0%)                         | 423 (46.7%)                             |
| Female                                 | 7745 (59.0%)                         | 483 (53.3%)                             |
| Country of birth                       |                                      |                                         |
| Sweden                                 | 11,523 (87.8%)                       | 797 (88.0%)                             |
| Other Nordic country                   | 681 (5.2%)                           | 36 (4.2%)                               |
| Non-Nordic EU27 country                | 340 (2.6%)                           | 27 (3.0%)                               |
| Non-EU27 country                       | 583 (4.4%)                           | 26 (2.9%)                               |
| Educational level                      |                                      |                                         |
| Data missing                           | 114 (0.9%)                           | 5 (0.6%)                                |
| Elementary                             | 4190 (31.9%)                         | 356 (39.3%)                             |
| Secondary school                       | 5844 (44.5%)                         | 396 (43.7%)                             |
| University                             | 2979 (22.7%)                         | 149 (16.4%)                             |
| Marital status                         |                                      |                                         |
| Married                                | 6885 (52.4%)                         | 432 (47.7%)                             |
| Previous comorbidities                 |                                      |                                         |
| Diabetes mellitus                      | 1104 (8.4%)                          | 96 (10.6%)                              |
| Obesity                                | 539 (4.1%)                           | 24 (2.6%)                               |
| Alcohol abuse                          | 567 (4.3%)                           | 66 (7.3%)                               |
| Ischemic heart disease                 | 1562 (11.9%)                         | 134 (14.8%)                             |
| Stroke                                 | 599 (4.6%)                           | 65 (7.2%)                               |
| Chronic obstructive pulmonary disease  | 531 (4.0%)                           | 51 (5.6%)                               |
| Peripheral vascular disease            | 276 (2.1%)                           | 28 (3.1%)                               |
| Renal disease                          | 225 (1.7%)                           | 33 (3.6%)                               |
| Cancer                                 | 1220 (9.3%)                          | 190 (21.0%)                             |
| Systemic steroid use                   |                                      |                                         |
| None                                   | 10,850 (82.7%)                       | 587 (64.8%)                             |
| Current (1–125 days)                   | 1114 (8.5%)                          | 244 (26.9%)                             |
| Former (>125 days)                     | 1163 (8.9%)                          | 75 (8.3%)                               |
| NSAID use                              |                                      |                                         |
| None                                   | 7166 (54.6%)                         | 466 (51.4%)                             |
| Current (1–125 days)                   | 2152 (16.4%)                         | 243 (26.8%)                             |
| Former (>125 days)                     | 3809 (29.0%)                         | 197 (21.7%)                             |
| Number of hospital stays 1–1095 days before index date |                     |                                         |
| 0                                      | 8075 (61.5%)                         | 425 (46.9%)                             |
| 1                                      | 2558 (19.5%)                         | 166 (18.3%)                             |
| 2                                      | 1050 (8.0%)                          | 116 (12.8%)                             |
| 3                                      | 520 (4.0%)                           | 72 (7.9%)                               |
| 4                                      | 333 (2.5%)                           | 44 (4.9%)                               |
| 5+                                     | 591 (4.5%)                           | 83 (9.2%)                               |
| Number of specialist consultations 1–365 days before index date |                     |                                         |
| 0+                                     | 5873 (44.7%)                         | 341 (37.6%)                             |
| 1–3                                    | 5141 (39.2%)                         | 304 (33.6%)                             |
| 4–6                                    | 1295 (9.9%)                          | 125 (13.8%)                             |
| 7–9                                    | 423 (3.2%)                           | 62 (6.8%)                               |
| 10+                                    | 395 (3.0%)                           | 74 (8.2%)                               |

The subgroup of cases that underwent emergency surgery, and the corresponding controls, are shown separately.
subgroup of 906 operated cases, 31.0% had been hospitalised during this period (mean in-hospital time 4.9 days, 95th percentile 30 days), as compared to 5.8% of their 8818 controls (mean in-hospital time 0.5 days, 95th percentile 1 day).

Discussion

The present study does not indicate a protective effect of statins on the risk of hospitalisation for colonic diverticular disease. In the first two regression models, current statin use was associated with an increased risk of hospitalisation for diverticular disease, a result likely to be influenced by residual confounding in these models. A subgroup analysis was consistent with a reduced risk of incident colonic diverticular disease requiring emergency surgery among current statin-users.

Strengths of the study include the population-based design, the large sample size, the complete coverage on statin exposure and the outcome, and the possibility to adjust for several potential confounders. Prospectively registered data with nationwide coverage were used, reducing the risk of selection bias and recall bias.

Several methodological limitations also exist. The validity of the diagnostic coding for colonic diverticular disease has not been determined on a nation-wide basis. However, a validation of ICD-10 codes K57.2-9 conducted on 528 consecutive patients at Danderyd Hospital (Stockholm, Sweden), showed that 95.8% had been correctly diagnosed with symptomatic diverticular disease [11]. Information was unavailable on whether dispensed drugs were actually used, and information on drug dispensing prior to 1 July 2005 was not available. Neither in-hospital drug administration nor use of over-the-counter NSAIDs could be accounted for (statins and systemic glucocorticoids are not available without prescription in Sweden). Study subjects who have spent time in hospital within 1–125 days before index date may have been exposed to statins during this period, while being classified as non-exposed in the present study. Since cases had been hospitalised to a greater extent than controls previous to the index date, bias may occur towards a negative OR. However, based on the amount of time spent in hospital by cases and controls, we expect that this would have a limited impact on the estimates. For the group of surgically treated patients, selection bias may be present. Patients with diverticular abscess and even some with distant intraperitoneal air can be treated non-operatively [26], and the frequency of statin use may differ in patients treated conservatively from patients subjected to surgery, e.g. due to the presence of comorbid conditions altering the threshold for a decision to operate a patient. Direct information on several known risk-factors for diverticular disease was not available, including diet, smoking, obesity and physical inactivity [10,11,27]. These may be associated with statin exposure, resulting in a biased estimate. On the other hand, use of preventive medication such as statins may be associated with a generally prevention-oriented behaviour, making healthy-user/adherer bias a concern [28]. The adjustment for several comorbidities and measures of healthcare utilisation is expected to reduce these sources of bias. Moreover, substituting
statins with glaucoma medication or prescribed vitamin B12 substitution, as “negative control exposures” not expected to be associated with symptomatic diverticular disease [25], did not yield OR estimates indicating an association of current drug exposure and the outcome. Nonetheless, the finding that former statin use was associated with an increased risk of hospitalisation for diverticular disease may reflect the presence of residual bias.

We are not aware of any previous study on the association between statin exposure and symptomatic diverticular disease including non-perforated cases. Our finding of a decreased risk for current statin users to undergo emergency surgery for diverticular disease is in accordance with the study of Humes et al., were a statin exposure was associated with a reduced risk of perforated colonic diverticular disease [13]. That was also a population-based case–control study using prospectively collected data, derived from general practitioners and hospital discharge letters. A notable difference is the lower frequency of “current” statin exposure reported by Humes et al., possibly reflecting differences in patterns of drug prescription – 0.78% of cases and 1.58% and of controls had a statin prescription between one and six months before index date.

The lipid-lowering class of drugs statins (HMG-CoA reductase inhibitors) is commonly used as secondary prevention in cardiovascular disease. Observational studies, as well as experimental animal studies, have indicated a beneficial effect of statins in sepsis [29]. Multiple possible mechanisms of action have been identified, including effects on cell signalling and leukocyte-endothelial cell interaction [30]. However, support from randomised controlled trials is lacking [31]. The apparent protective effect of statins only on diverticular disease requiring surgery may reflect a possible effect of statins on sepsis, rather than on the development of diverticular disease itself, since septic patients may be less likely to be treated conservatively.

In conclusion, this large population-based case–control study does not support our hypothesis that statins may have a preventive effect on the development of symptomatic diverticular disease. In the subgroup of patients subjected to surgery, however, current statin exposure was associated with a reduced risk. Given the observational nature of the study and the presence of unmeasured confounders, the results should be interpreted with caution.

Declaration of interest: The study was supported by the Emil and Wera Cornell Foundation. Ola Olén was funded by the Swedish Medical Society and The Bengt Ihre Fellowship in gastroenterology when working on this project. None of the funding organisations has had any role in the design and conduct of the study; in the collection, management and analysis of the data; or in the preparation, review and approval of the manuscript.

References

[1] Stollman N, Raskin JB. Diverticular disease of the colon. Lancet 2004;363:631–9.
[2] Strate LL, Modi R, Cohen E, Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol 2012;107:1486–93.
[3] Jacobs DO. Clinical practice. Diverticulitis. N Engl J Med 2007;357:2057–66.
[4] Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H, et al. Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis. Dig Surg 2013;30:278–92.
[5] Erichsen R, Strate L, Sørensen HT, Baron JA. Positive predictive values of the International Classification of Disease, diagnoses codes for diverticular disease in the Danish National Registry of Patients. Clin Exp Gastroenterol 2010;3:139–42.
[6] Lorimer JW, Doumit G. Comorbidity is a major determinant of severity in acute diverticulitis. Am J Surg 2007;193:681–5.
[7] Granlund J, Svensson T, Olen O, Hjem F, Pedersen NL, Magnusson PK, et al. The genetic influence on diverticular disease – a twin study. Aliment Pharmacol Ther 2012;35:1103–7.
[8] Strate LL, Erichsen R, Baron JA, Mortensen J, Pedersen JK, Riis AH, et al. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. Gastroenterology 2013;144:736–42e1; quiz e14.
[9] Aldoori WH, Giovannucci EL, Rockett HR, Sampson L, Rimm EB, Willett WC. A prospective study of dietary fiber types and symptomatic diverticular disease in men. J Nutr 1998;128:714–19.
[10] Hjem F, Wolk A, Hakansson N. Obesity, physical inactivity, and colonic diverticular disease requiring hospitalization in women: a prospective cohort study. Am J Gastroenterol 2012;107:296–302.
[11] Hjem F, Wolk A, Hakansson N. Smoking and the risk of diverticular disease in women. Br J Surg 2011;98:997–1002.
[12] Kvasnovsky CL, Papagrigoriadis S, Bjarnason I. Increased diverticular complications with nonsteroidal anti-inflammatory drugs and other medications: a systematic review and meta-analysis. Colorectal Dis 2014;16:O189–96.
[13] Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population-based case–control study. Gut 2011;60:219–24.
[14] Suzuki S, Tajima T, Sassa S, Kudo H, Okayasu I, Sakamoto S. Preventive effect of fluvastatin on ulcerative colitis-associated carcinogenesis in mice. Anticancer Res 2006;26:4223–8.
[15] Oishi M, Tokuhara K, Miki H, Tanaka Y, Yamaki S, Kaibori M, et al. Temporal and spatial dependence of inflammatory biomarkers and suppression by fluvastatin in dextran
sodium sulfate-induced rat colitis model. Dig Dis Sci 2014;59:2126–35.

[16] Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659–67.

[17] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.

[18] Statistics Sweden. Registret över totalbefolkningen [Swedish Register of the Total Population]. Available from: http://www.scb.se/Pages/List___257499.aspx [last accessed Jan 2015].

[19] Wettermark B, Hammar N, Michael Fored C, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register – opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Safe 2007;16:726–35.

[20] WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015. Available from: http://www.whocc.no/atc_ddd_index/ [last accessed January 2015].

[21] The National Board of Health and Welfare, Sweden. Dödsorsaksstatistik – Historik, produktionsmetoder och tillförlitlighet. [Cause-of-death statistics – history, production and reliability]. 2010. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18019/2010-4-33.pdf [last accessed January 2015].

[22] Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48:27–33.

[23] Statistics Sweden. Registret över befolkningens utbildning [The register of education]. Available from: http://www.scb.se/sv_/Vara-tjanster/SCBs-data-for-forskning/SCBs-datalager/Registret-over-befolkningens-utbildning-/ [last accessed Jan 2015].

[24] The National Board of Health and Welfare, Sweden. Klassifikation av kirurgiska åtgärder 1997 (Reviderad november 2004) [Swedish version of Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures 1997 (Revised 2004)]. 2004. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10244/2004-4-1_200441.pdf [last accessed Jan 2015].

[25] Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010;21:383–8.

[26] Sallinen VJ, Mentula PJ, Leppäniemi AK. Nonoperative management of perforated diverticulitis with extraluminal air is safe and effective in selected patients. Dis Colon Rectum 2014;57:875–81.

[27] Crowe FL, Appleby PN, Allen NE, Key TJ. 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. BMJ 2011;343:d4131.

[28] Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med 2011;26:546–50.

[29] Terblanche M, Almoq Y, Rosenson RS, Smith TS, Hackam DG. Statins: panacea for sepsis? Lancet Infect Dis 2006;6:242–8.

[30] Terblanche M, Almoq Y, Rosenson RS, Smith TS, Hackam DG. Statins and sepsis: multiple modifications at multiple levels. Lancet Infect Dis 2007;7:358–68.

[31] Pasin L, Landoni G, Castro ML, Cabrini L, Belletti A, Feltracco P, et al. The effect of statins on mortality in septic patients: a meta-analysis of randomized controlled trials. PLoS One 2013;8:e82775.

Supplementary materials available online