Smoking and the Risk of Hospitalization for Symptomatic Diverticular Disease: A Population-Based Cohort Study from Sweden

David J. Humes, B.Sc., M.B.B.S., Ph.D., F.R.C.S.1,5 • Jonas F. Ludvigsson, Ph.D.2,3
Bengt Jarvholm, M.D., Ph.D.4

1 Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, City Hospital, Nottingham, United Kingdom
2 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
3 Department of Paediatrics, Örebro University Hospital, Örebro, Sweden
4 Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
5 Nottingham Digestive Diseases Biomedical Research Unit, University of Nottingham, Nottingham, United Kingdom

BACKGROUND: Current studies reporting on the risk of smoking and development of symptomatic diverticular disease have reported conflicting results.

OBJECTIVE: The aim of this study was to investigate the association between smoking and symptomatic diverticular disease.

DESIGN: This is a cohort study

SETTINGS: Information was derived from the Swedish Construction Workers Cohort 1971–1993.

PATIENTS: Patients were selected from construction workers in Sweden.

MAIN OUTCOME MEASURES: The primary outcome measured was the development of symptomatic diverticular disease and complicated diverticular disease (abscess and perforation) as identified in the Swedish Hospital Discharge Register. Adjusted relative risks of symptomatic diverticular disease according to smoking status were estimated by using negative binomial regression analysis.

RESULTS: In total, the study included 232,685 men and 14,592 women. During follow-up, 3891 men and 318 women had a diagnosis of later symptomatic diverticular disease. In men, heavy smokers (≥15 cigarettes a day) had a 1.6-fold increased risk of developing symptomatic diverticular disease compared with nonsmokers (adjusted relative risk, 1.56; 95% CI, 1.42–1.72). There was evidence of a dose-response relationship, because moderate and ex-smokers had a 1.4- and 1.2-fold increased risk compared with nonsmokers (adjusted relative risk, 1.39; 95% CI, 1.27–1.52 and adjusted relative risk, 1.14; 95% CI, 1.04–1.27). These relationships were similar in women, but the risk estimates were less precise owing to smaller numbers. Male ever-smokers had a 2.7-fold increased risk of developing complicated diverticular disease (perforation/abscess) compared with nonsmokers (adjusted relative risks, 2.73; 95% CI, 1.69–4.41).

LIMITATIONS: We were unable to account for other confounding variables such as comorbidity, prescription medication, or lifestyle factors.

CONCLUSIONS: Smoking is associated with symptomatic diverticular disease in both men and women and with an increased risk of developing complicated diverticular disease.

KEY WORDS: Diverticular disease; Smoking; Complicated diverticular disease.

Diverticular disease and its associated complications such as acute diverticulitis place a significant burden on health care services. This burden is expected to increase as the population ages, with an already reported increase in the occurrence of the most serious complication perforation and hospitalization for acute diverticulitis. Given these in-
creases, there has been interest in possible causal factors that could be modified to prevent these complications, such as smoking. There are biologically plausible reasons why tobacco use may be important in the pathogenesis of symptomatic disease, because tobacco use impairs immune function, alters gut transit times, reduces blood flow, and is associated with other intestinal inflammatory conditions. A small retrospective study of 80 patients reported an association between smoking and an increased risk of diverticular complications. A further small retrospective study reported an increased risk of stricture and perforation in patients undergoing elective colectomy for diverticular disease among smokers. A larger population-based study of women reported a 1.23-fold increased risk (relative risk (RR), 1.23; 95% CI, 0.99–1.52) in current smokers of symptomatic diverticular disease when accounting for other confounding factors compared with nonsmokers. The study also reported a greater risk of developing a perforation or abscess in current smokers compared with nonsmokers (RR, 1.89; 95% CI, 1.15–3.10). However, a study of the American Health Care Professionals cohort found no increased association between smoking and symptomatic diverticular disease when accounting for other confounding factors in men. Current studies, therefore, do not provide population-based evidence of an association between smoking and symptomatic diverticular disease and have failed to demonstrate a dose-response relationship. The aim of this study was to assess the relationship between smoking and development of symptomatic and complicated diverticular disease in a cohort of Swedish construction workers.

MATERIALS AND METHODS

Patients and Data Sources
The Swedish construction workers cohort is a population-based prospective cohort of 389,132 individuals of whom 369,174 were men and 19,418 were women. They had participated in health examinations from 1971 to 1993. On entry to the cohort, data were collected on smoking, occupation description, and BMI by the administration of a questionnaire. Through the personal identity number, we linked these data with data from the Swedish Hospital Discharge Register. The baseline examination data were taken as the baseline data for the current study. Persons with unknown BMI or unknown smoking habits were excluded (n = 80,451) as were those born before 1908 (n = 1038), ie, older than 79 years in 1987, as were those who died or emigrated before 1987 (n = 20,824).

Follow-up
Study follow-up started from the first recorded health examination and continued until death or December 2013. National coverage of the Swedish Hospital Discharge Register became complete from 1987. We therefore undertook a sensitivity analysis that included only those having health examinations between 1987 and 1993 as a start date to the end of follow-up to ensure the relationships observed remained.

Outcome Definition
Hospitalization for symptomatic diverticular disease was defined as any patient with a World Health Organization International Classification of Diseases (ICD) code for diverticulitis K57, 562 (International Classification of Diseases, 10th Revision (ICD-10)) and 562 (International Classification of Diseases, 9th Revision (ICD-9)). Perforated diverticular disease and diverticular abscess were defined as complicated diverticular disease by using ICD-10 code K57.0, K57.2, K57.4, K57.6, or K57.8 and restricted to cases occurring from 1997 to 2013. The first outcome noted in the register for symptomatic or complicated disease was used in the analyses.

Exposures
We categorized smoking into 4 groups: nonsmokers, ex-smokers, moderate (≤14 cigarettes per day or equivalent), and heavy smokers (≥15 cigarettes per day). A previous review of smoking data at the first and second health examination (2–3 years apart) among 18,593 subjects in the “Bygghälsan” cohort found a 89% perfect match with data. Inconsistencies regarding never-smoking status (study participants first indicated that they were current/former smokers in 1 questionnaire and then reported never smoking in the second questionnaire) were reported for 2.7%. We categorized BMI into 18.5 to 19.9 kg/m², 20.0 to 24.9 kg/m², 25 to 29.9 kg/m², 30 to 34.9 kg/m², and ≥35 kg/m². This information was recorded from the first visit of the patient at baseline. As a marker for socioeconomic status, we used job description, dividing the cohort into office workers, foremen, skilled workers, and unskilled/semiskilled workers. Men with an unspecified job title were excluded from the analysis (n = 39,532), whereas the majority of women with manual jobs had an unspecified job title and were included in the unskilled/semi-skilled category. All workers were employed in the construction industry.

Statistical Analysis
Person-years of follow-up were calculated for each person from year of health examination within the construction worker service through December 31, 2013, symptomatic diverticular disease, death, or emigration, whichever occurred first. The person-years were stratified for age...
(10-year age strata), sex, BMI, socioeconomic status, tobacco smoking, and lag time. We studied age intervals from 20 to 79 years for men, but, owing to the few cases in young women, we restricted that analysis to 40 to 79 years in women. Lag time was the time between health examination and time of follow-up and was categorized in 10-year classes (0–9, 10–19, 20–29, and 30+ years).

Relative risks were estimated by negative binomial regression analysis, and 95% confidence intervals were calculated by standard errors. We planned a sensitivity analysis for those examined between 1987 and 1993 when coverage of the inpatient register became universal. We used statistics software SAS 9.3 (SAS Institute, Cary, NC) to perform the statistical tests.

p values of <0.05 were considered statistically significant and all p values shown are 2-sided.

Ethics
The study was approved by the Regional Ethical Review Board in Umeå (2014-195-32M) and the board of the Swedish construction workers cohort.

RESULTS
Demographics of Cohort
In total, the study included 232,685 men and 14,592 women. We identified 4209 individuals with a diagnosis of symptomatic diverticular disease with 3891 men and 318 women. The median total follow-up time was 30 years for men and 29 years for women. Men were less likely to develop symptomatic diverticular disease than women when accounting for age, BMI, smoking, lag time, and socioeconomic status (adjusted RR (aRR), 0.68; 95% CI, 0.59–0.78). The baseline demographics of the male and female smoking groups are shown in Table 1.

Smoking and Symptomatic Diverticular Disease
Heavy smoking in men was associated with an increased risk of developing symptomatic diverticular disease (RR, 1.63; 95% CI, 1.43–1.85) (Table 2) compared with nonsmokers. In the adjusted analysis, this figure was attenuated but still represented a 1.6-fold increased risk (aRR, 1.56; 95% CI, 1.42–1.72). There was a dose-response relationship with those smoking less than 15 cigarettes a day and ex-smokers having a lower risk of developing symptomatic diverticular disease compared with nonsmokers (<15 cigarettes a day aRR, 1.39; 95% CI, 1.27–1.52 and ex-smokers aRR, 1.14; 95% CI, 1.04–1.27).

In women, the number of cases and the precision of risk estimates were lower. Only moderate smokers had a statistically increased risk of developing symptomatic diverticular disease with a 1.6-fold increase compared with nonsmokers (aRR, 1.64; 95% CI, 1.25–2.14) (Table 2).

Smoking and Complicated Diverticular Disease (Perforation/Abscess)
Examination of the association between smoking and complicated diverticular disease was not possible in women because there were too few cases. In male ever-smokers, we found an increased risk of diverticular abscess or perforation of 2.7-fold compared with nonsmokers (aRR, 2.73; 95% CI, 1.69–4.41) (Table 3). There was again evidence of a dose-response relationship with heavy smokers having a 3.8-fold increase compared with nonsmokers (adjusted HR, 3.80; 95% CI, 2.21–6.51), although the precision of this estimate was lower owing to fewer outcomes.

Sensitivity Analysis of Men Examined From 1987 to 1993
Restricting the analysis to those men with health examinations between 1987 and 1993 demonstrated a similar relationship between smoking and symptomatic diverticular

Table 1. Demographics of men and women by smoking classification

|                | Nonsmokers | Ex-smokers | Moderate smokers | Heavy smokers |
|----------------|------------|------------|------------------|---------------|
| **Men**        |            |            |                  |               |
| N              | 102,486    | 36,133     | 55,807           | 38,259        |
| Year of birth (SD) | 1951.6 (16.4) | 1938.1 (14.7) | 1940.3 (15.7) | 1946.3 (13.4) |
| Mean BMI, kg/m² (SD) | 24.0 (3.1) | 24.9 (3.1) | 23.9 (3.0) | 24.0 (3.2) |
| Worker level    |            |            |                  |               |
| Office worker, n (%) | 3780 (3.7) | 1597 (4.4) | 1315 (2.4) | 1403 (3.7) |
| Foreman, n (%)   | 9663 (9.4) | 3947 (10.9) | 4169 (7.5) | 3717 (9.7) |
| Skilled worker, n (%) | 76,285 (74.4) | 24,576 (68.0) | 40,844 (73.2) | 25,531 (66.7) |
| Unskilled/semiskilled, n (%) | 12,758 (12.4) | 6013 (16.6) | 9479 (17.0) | 7608 (19.9) |
| **Women**       |            |            |                  |               |
| N              | 7317       | 1349       | 3274             | 2652          |
| Year of birth (SD) | 1945.3 (15.9) | 1944.2 (11.9) | 1945.4 (13.9) | 1948.0 (12.1) |
| Mean BMI, kg/m² (SD) | 23.6 (4.0) | 23.7 (3.7) | 22.7 (3.5) | 23.0 (3.6) |
| Worker level    |            |            |                  |               |
| Office worker, n (%) | 3254 (44.5) | 672 (49.8) | 1413 (43.2) | 1046 (39.4) |
| Foreman, n (%)   | 331 (4.5) | 22 (1.6) | 59 (1.8) | 68 (2.6) |
| Skilled worker, n (%) | 359 (4.9) | 33 (2.5) | 154 (4.7) | 183 (6.9) |
| Unskilled/semiskilled, n (%) | 3373 (46.1) | 622 (46.1) | 1648 (50.3) | 1355 (51.1) |
disease with heavy smokers having a 1.8-fold increased risk of symptomatic diverticular disease compared with nonsmokers (aRR, 1.79; 95% CI, 1.43–2.23).

**DISCUSSION**

We found that smoking is associated with an increased risk of developing symptomatic diverticular disease in both men and women. Those men smoking more than or equal to 15 cigarettes a day had a 1.6-fold increased risk of developing symptomatic diverticular disease requiring hospitalization in comparison with nonsmokers. In men, there was also a 2.7-fold increase risk in the development of complicated diverticular disease in ever-smokers in comparison with nonsmokers.

Two small retrospective studies have reported an increased risk of diverticular complications in smokers.\(^\text{10,11}\) These studies, however, did not report on the development of symptomatic disease. Two population-based studies have reported conflicting results as to the role of smoking in the development of symptomatic disease. Aldoori et al\(^\text{13}\) reported current smoking was not significantly associated with symptomatic diverticular disease (RR, 1.25; 95% CI, 0.75–2.09), but the cohort studied was formed of male health care workers with only 10% of the cohort being current smokers. The study also lacked power because the analysis of smoking was based on only 45 events as opposed to the 4209 events in our study. A study reporting on the risk of symptomatic diverticular disease from the Swedish Mammography cohort reported a 1.26-fold increase in risk of symptomatic diverticular disease in current smokers compared with nonsmokers, and they were unable to report a dose-response relationship.\(^\text{12}\) Our current estimates are greater than these with a 1.6-fold increase in risk of symptomatic disease in those smoking more than 15 cigarettes a day compared with nonsmokers.

We report for the first time a dose-response relationship with increasing risk of symptomatic diverticular disease with increasing frequency of tobacco use. The risk was greatest in those who were heavy smokers. Women who smoke have been reported to have a 1.9-fold increased risk of diverticular abscess and perforation.\(^\text{12}\) Those smoking more than 10 cigarettes a day had the greatest increase in risk (RR, 2.30; 95% CI, 1.26–4.20).\(^\text{12}\) Other studies have also shown an increased risk of perforation associated with smoking.\(^\text{18,19}\)

This is a large cohort study with the use of standardized questionnaires to prospectively collect data on smoking, limiting the potential for recall bias. Because we have used only the first questionnaire collected, there is a possibility of nondifferential misclassification of current and ex-smokers; however, previous work has reported that the data on smoking remained similar between the first and second health questionnaires that were administered 2 to 3 years apart in

### Table 2. All cases of symptomatic diverticular disease (SDD) in men and women examined 1971 to 1993

| Tobacco smoking   | Person-years | Cases of SDD | Unadjusted RR (95% CI) | Adjusted RR (95% CI)\(^a\) |
|-------------------|--------------|--------------|------------------------|---------------------------|
| **Men**           |              |              |                        |                           |
| Nonsmokers        | 2,753,953    | 1219         | 1 (ref)                | 1 (ref)                   |
| Ex-smokers        | 849,666      | 682          | 1.42 (1.24–1.63)       | 1.14 (1.04–1.27)          |
| Moderate smokers <15 cig/day | 1,308,270 | 1146         | 1.62 (1.43–1.84)       | 1.39 (1.27–1.52)          |
| Heavy smokers ≥15 cig/day | 1,004,439 | 844          | 1.63 (1.43–1.85)       | 1.56 (1.42–1.72)          |
| **Women**         |              |              |                        |                           |
| Nonsmokers        | 163,065      | 133          | 1 (ref)                | 1 (ref)                   |
| Ex-smokers        | 31,605       | 37           | 1.35 (0.86–2.11)       | 1.33 (0.92–1.92)          |
| Moderate smokers <15 cig/day | 74,170       | 97           | 1.64 (1.15–2.35)       | 1.64 (1.25–2.14)          |
| Heavy smokers ≥15 cig/day | 61,689      | 51           | 0.97 (0.65–1.47)       | 1.12 (0.81–1.55)          |

\(\text{cig} = \text{cigarettes}; \text{RR} = \text{relative risk.}\)

\(\text{aAdjusted for age, BMI, lag time, and socioeconomic status.}\)

### Table 3. Association of smoking with complicated diverticular disease (CDD) (abscess/perforation)

| Tobacco smoking   | Person-years | Cases of CDD | Unadjusted RR (95% CI) | Adjusted RR (95% CI)\(^a\) |
|-------------------|--------------|--------------|------------------------|---------------------------|
| Nonsmokers        | 1,713,459    | 25           | 1 (ref)                | 1 (ref)                   |
| Ex-smokers        | 482,036      | 17           | 1.43 (0.77–2.70)       | 1.55 (0.80–2.99)          |
| Moderate smokers <15 cig/day | 742,908 | 45           | 2.79 (1.70–4.59)       | 2.80 (1.64–4.77)          |
| Heavy smokers ≥15 cig/day | 599,172 | 42           | 3.75 (2.28–6.16)       | 3.80 (2.21–6.51)          |

\(\text{cig} = \text{cigarettes}; \text{RR} = \text{relative risk.}\)

\(\text{aAdjusted for age, BMI, lag time, and socioeconomic status.}\)
89% of the cases reviewed. The diagnosis of symptomatic diverticular disease was made by using ICD-10 and ICD-9 coding. This has limited our ability to identify cases of acute diverticulitis because acute diverticulitis is not included in the ICD-10 classification; however, we have been able to stratify into those with abscess/perforation and shown an increased risk of complicated disease in men who smoke. A review of National Patient Register validation studies conducted by Ludvigsson et al concluded that the positive predictive value varies based on the diagnosis, but it generally ranges between 85% and 95%. Furthermore, a review of coding of symptomatic diverticular disease using the K572-9 code in 528 consecutive admissions to a single center in Sweden found that 95.8% of all cases were classified correctly. We have not been able to account for comorbidity, dietary, and lifestyle factors. However, previous small studies adjusting for these factors have shown they are only weak risk factors. Coverage of the inpatient register became universal in 1987, and our sensitivity analysis demonstrated broadly similar associations with our analysis of those with a first examination performed from 1971 to 1993. We excluded those over the age of 79 years (>79 years) because the association observed may differ for persons of increased age. All cases identified in this study required hospitalization for their diverticular disease. It is likely that some patients with symptomatic disease will have been treated as out-patients or in the community, and, therefore, the current study does not allow us to report on the association between smoking and symptomatic disease in this group.

Our findings strengthen the hypothesis that smoking is associated with the development of symptomatic diverticular disease. Given these findings, it may be advisable for patients diagnosed with colonic diverticulosis to abstain from smoking to reduce their risk of developing symptomatic disease.

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