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Significant association between the use of different proton pump inhibitors and microscopic colitis: a nationwide Danish case-control study

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Summary

Background: Microscopic colitis causes chronic watery diarrhoea and has previously been associated with the use of proton pump inhibitors.

Aim: To explore the association between proton pump inhibitor use and microscopic colitis, including its dependency on timing, dose and choice of proton pump inhibitor.

Methods: Within a 10-year period, we identified 10 652 patients with a first-time diagnosis of microscopic colitis, including 6254 (59%) with collagenous colitis and 4398 (41%) with lymphocytic colitis. All microscopic colitis cases were histologically confirmed in the Danish Pathology Register. Information on proton pump inhibitor use was obtained from the Danish Prescription Register. In this case-control study, we estimated the adjusted odds ratios (aOR) for the association between proton pump inhibitor use and risk of microscopic colitis using conditional logistic regression while adjusting for potential confounders.

Results: We found strong associations between current proton pump inhibitor use and both collagenous colitis (aOR 6.98; 95% CI: 6.45-7.55) and lymphocytic colitis (aOR 3.95; 95% CI: 3.60-4.33). This association was observed with all PPIs. The strongest association was with the current use of lansoprazole for both collagenous colitis (aOR 15.74; 95% CI: 14.12-17.55) and lymphocytic colitis (aOR 6.87; 95% CI: 6.00-7.86). When considering timing, ORs were highest for current use of proton pump inhibitor and lower for recent or past exposure. No clear dose-response pattern was observed.

Conclusions: We found a strong association between microscopic colitis and ongoing use of proton pump inhibitors, especially lansoprazole.

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1 | INTRODUCTION

Microscopic colitis is characterised by chronic diarrhoea in patients with macroscopically normal or near-normal mucosa at colonoscopy. Thus, diagnosis relies on specific histological findings in colon biopsies. Microscopic colitis consists of two main entities, lymphocytic colitis and collagenous colitis.[1] The two subtypes share histopathological features, characterised by a marked increase in intraepithelial lymphocytes, and a thickened subepithelial collagen band additionally characterises collagenous colitis.[2] Epidemiological studies have shown that microscopic colitis has been diagnosed more frequently in recent decades. In a recent Danish study, we reported a continuous increase in the incidence rates of microscopic colitis from 4.6 to 24.7 per 100 000 person-years from 2002 to 2011.[3] However, the aetiology of microscopic colitis is largely unknown and its pathogenesis is not well described. Diversion of the faecal stream with a temporary ileostomy in patients with collagenous colitis results in the resolution of histological changes in the colonic mucosa, indicating luminal factors in its pathogenesis.[4] Furthermore, a variety of factors are suspected, and drug consumption has been suggested to act as an environmental risk factor and has been implicated as a causative or triggering agent of microscopic colitis.[5] Moreover, the use of proton pump inhibitors (PPI) has increased rapidly within recent decades,[6] and the association between PPI use and microscopic colitis has been consistently replicated in a number of studies.[7-9] In a previous study, we demonstrated an increased odds ratio (OR) for microscopic colitis in patients with prescriptions for PPIs, but we were unable to differentiate between individual PPIs.[7] However, some important aspects of this association have been poorly elucidated.[10] First, it is unclear whether the association between PPI and microscopic colitis applies equally to lymphocytic colitis and collagenous colitis. Second, some studies have suggested a specific risk with lansoprazole.[11, 12] However, this finding is predominantly based on case reports or small-scale case-control studies; large-scale studies, which include validated outcomes, are lacking. Third, the pattern of PPI use that is most likely to produce microscopic colitis is unknown; for example, is there a dose-response effect and/or an association with timing of PPI use? Finally, the magnitude of the risk has not been adequately described. In light of the sparse evidence for these aspects, we conducted new analyses in an updated and extended version of our dataset based on high-quality Danish Health Registries to examine the risk of microscopic colitis between different PPIs, effect of timing of PPI use and dependency on PPI dose. Furthermore, we explored the potential differences between collagenous colitis and lymphocytic colitis.

2 | MATERIALS AND METHODS

Based on Danish registries, we performed a population-based case-control study of PPI use and risk of microscopic colitis. Cases included patients with a histologically confirmed diagnosis of microscopic colitis from 2004 to 2013, and control patients were recruited from the background population using a risk-set sampling technique.

2.1 | Data sources

Medical histories and information on drug exposure were obtained for both cases and controls using data extracted from the following four Danish registries with a nationwide coverage of approximately 5.6 million inhabitants: the Danish Pathology Register, Danish Person Registry, Danish National Patient Register and Danish Prescription Register.

The *Danish Pathology Register* was established in 1990, and in 1997, it became mandatory for all pathology departments in Denmark to report their pathological findings to this register. Diagnoses were encoded according to a Danish modification of the Systematized Nomenclature of Medicine (SNOMED).[13] The data included all pathological data in Denmark.

The *Danish Civil Registration System* was established in 1968, and since then, all Danish residents have been assigned a 10-digit personal identifier. This unique civil registry number, which encodes information on sex and birthdate, is used in virtually all Danish registries, thereby permitting unambiguous data linkage.[14] This Danish Person Register also consists of data on migrations, births and death, which enable the identification of eligible controls and the ability to track the residency of all subjects, thus ensuring opportunities to perform a complete follow-up.

The *Danish National Patient Register* was established in 1977 and includes the civil registry number and in-patient discharge diagnoses. Since 1995, the register has also included out-patient diagnoses. All diagnoses are encoded by medical doctors according to the Danish versions of the International Classification of Diseases (ICD-8 from 1977 to 1993 and ICD-10 since 1994).[15]

The *Danish Prescription Register* was established in 1995 and retains key information on all prescriptions dispensed from all Danish pharmacies.[16] The register includes the civil registration number of the patient, the date of dispensation and a full account of the dispensed product, including the anatomical therapeutic chemical (ATC) code, quantity expressed by the defined daily dose (DDD) and date of dispensation.[17] Using this registry, a complete and time-reliable drug prescription history can be established for each individual.

2.2 | Cases

Our case population included all patients with a first recorded diagnosis of either collagenous colitis (SNOMED code: S62536) or lymphocytic colitis (SNOMED code: S62533) in the Danish Pathology Register from January 2004 to December 2013. The date of a first recording of one of these diagnoses was defined as the case index date.

2.3 | Controls

For each microscopic colitis case, we randomly sampled 10 controls using the Danish Civil Registration System and applied a risk-set sampling technique. We required that each control matched the corresponding case with respect to birth year and sex. Controls were assigned an index date that was identical to that of the corresponding cases. Thus, the calculated odds ratios are unbiased estimates of the incidence rate ratio, which emerged from a cohort study based on the same source population.

2.4 | Exposure to PPIs

For both cases and controls, PPI exposure was defined by the redemption of prescription for PPIs recorded in the Danish Prescription Registry prior to the index dates. We used the following ATC codes to define PPIs: A02BC any PPIs; A02BC01 omeprazole; A02BC02 pantoprazole; A02BC03 lansoprazole; A02BC04 rabeprazole; A02BC05 esomeprazole. Other PPIs have not been marketed in Denmark.

Current users of PPIs were defined as having redeemed a prescription of PPI within 90 days prior to their index date. For current users of PPIs, we calculated the cumulative amount dispensed in the last 365 days preceding the index date as a proxy for their daily intake. *Recent users* were defined as having redeemed at least one prescription of PPI in the period of 91-365 days prior to their index date but none within the last 90 days. *Past users* received their last prescription more than 365 days prior to their index date. *Never users* had no recorded PPI prescriptions at any time before their index date.

2.5 | Confounders

Confounders were selected based on an automated empiric procedure. First, we selected a wide array of candidate variables, that is, all of the characteristics listed in Table 1. For each of these variables, we then calculated the OR for current PPI use in a model with or without the candidate variable included in addition to current PPI use. If the OR for PPI use changed by more than 5% in either direction by including the candidate variable, we selected the candidate variable among the potential confounders that were controlled.[18] Thus, factors that empirically behaved as confounders were included from the list. In addition, we forced current use of NSAID into the list of confounders, as we expected this feature to exert a confounding effect, as it was both a risk factor for microscopic colitis and an indication for the prescription of PPIs.[8] Age, sex and calendar time were inherently adjusted using the matching procedure.

2.6 | Statistical analyses

The analysis conformed to a conventional matched case-control approach. We used conditional logistic regression to estimate the OR with the 95% confidence interval (CI) associating PPI use with microscopic colitis while adjusting for selected confounders as previously described. Unless otherwise specified, patients who had never used PPI were used as references for all analyses.

A number of prespecified analyses were performed: (a) a characterisation of cases vs controls in terms of a past history of discharge diagnoses and concurrent use of coprescribed medication. We defined concurrent use as any prescription occurring within the past 90 days before the index date; (b) analysis for each of the individual PPIs; (c) analysis from which all subjects who had a history of use for more than one PPI was excluded. This information was intended to serve as a supportive analysis to determine whether there was a different OR for different PPIs. By excluding subjects with a history of more than one PPI, we avoided potential carry-over between periods of use for different PPIs; (d) analyses according to current, recent and past use of PPIs; (e) analyses according to the outcomes of either collagenous colitis or lymphocytic colitis; (f) analyses according to the cumulative amount of PPIs dispensed during the last 365 days prior to the index date. Only current users were considered as exposures in this analysis. The intention was to reflect the daily amount of PPI taken; and (g) an analysis to characterise the potential interaction between PPI and NSAID as a risk factor for microscopic colitis.

In addition, we performed two post hoc analyses after observing a specifically high OR for lansoprazole: (a) a formal case-control analysis to determine whether the OR for lansoprazole was significantly higher than any other PPIs. Only current users of PPIs were included. The exposure was the current use of lansoprazole, and the reference was the current use of any other PPI and (b) an analysis of determinants for the selection of lansoprazole over other PPIs. This parameter was intended to provide information on potential confounders that might account for the particularly strong association with lansoprazole.

2.7 | Approval

The conduct of this study was approved by the Danish Data Protection Agency (J.nr.2014-41-3214). Approval by the Ethics Committee is not required in register-based research, such as this study. Informed consent from participants was not required.

3 | RESULTS

During a 10-year period from January 2004 to December 2013, we identified 10 652 patients with a first-time recorded diagnosis of microscopic colitis in the Danish Pathology Register, including 6250 (59%) patients with collagenous colitis and 4402 (41%) patients with lymphocytic colitis. Characterisation of cases and controls in terms of age, sex, PPI use and a variety of comorbid conditions as well as coprescribed medication are shown in (Table 1). Age at the time of diagnosis was slightly lower in lymphocytic colitis cases (66 years) compared to collagenous colitis cases (68 years). There was a female majority in both groups, which was more pronounced in collagenous

TABLE 1 Basic characteristics of 10,652 cases of microscopic colitis and the matched controls. Current drug use: Prescription of drug within 90 days prior to the index date

	CC cases N = 6250	CC controls N = 59 842	LC cases N = 4402	LC controls N = 41 539
Demographics				
Female	4724 (76%)	45 350 (76%)	2847 (65%)	26 668 (64%)
Age, median (interquartile range)	68 (59-77)	68 (59-77)	66 (56-75)	66 (56-74)
Current drug use				
Any proton pump inhibitor	2470 (40%)	6088 (10%)	1267 (29%)	3791 (9%)
Omeprazole	285 (5%)	1528 (3%)	208 (5%)	882 (2%)
Pantoprazole	359 (6%)	1764 (3%)	310 (7%)	1166 (3%)
Lansoprazole	1712 (27%)	1923 (3%)	659 (15%)	1234 (3%)
Esomeprazole	257 (4%)	1020 (2%)	175 (4%)	602 (1%)
Nonsteroid anti-inflammatory drug	1342 (21%)	6949 (12%)	682 (15%)	4482 (11%)
Anticoagulants	227 (4%)	1910 (3%)	164 (4%)	1209 (3%)
Platelet inhibitors	1683 (27%)	10 063 (17%)	964 (22%)	6436 (15%)
Digoxin	437 (7%)	2829 (5%)	285 (6%)	1669 (4%)
Antihypertensives	3287 (53%)	24 417 (41%)	2065 (47%)	15 299 (37%)
Lipid-lowering drugs	1489 (24%)	10 452 (17%)	967 (22%)	6948 (17%)
Bisphosphonates	407 (7%)	2638 (4%)	188 (4%)	1409 (3%)
Benzodiazepines	1376 (22%)	7150 (12%)	829 (19%)	4219 (10%)
Antidepressants	1362 (22%)	6313 (11%)	1087 (25%)	3939 (9%)
Upper gastrointestinal disease				
Gastro-oesophageal reflux disease	124 (2%)	157 (0%)	58 (1%)	108 (0%)
Gastroduodenal ulcer	131 (2%)	211 (0%)	68 (2%)	146 (0%)
Gastroduodenitis	127 (2%)	173 (0%)	83 (2%)	101 (0%)
Coeliac disease	92 (1%)	127 (0%)	83 (2%)	85 (0%)
Cancer				
Gastrointestinal cancer (total)	133 (2%)	1212 (2%)	82 (2%)	742 (2%)
Colon cancer	98 (2%)	724 (1%)	42 (1%)	442 (1%)
Lung cancer	37 (1%)	306 (1%)	18 (0%)	180 (0%)
Thyroid disease				
Hypothyroidism	2396 (38%)	15494 (26%)	1555 (35%)	10417 (25%)
Hyperthyroidism	204 (3%)	1491 (2%)	124 (3%)	898 (2%)
Diabetes				
Type 1 Diabetes mellitus	220 (4%)	1183 (2%)	139 (3%)	844 (2%)
Type 2 Diabetes mellitus	420 (7%)	3035 (5%)	263 (6%)	1984 (5%)
Vascular diseases				
Hypertension	1653 (26%)	9969 (17%)	991 (23%)	6190 (15%)
Ischaemic heart disease	1275 (20%)	6526 (11%)	807 (18%)	4371 (11%)
Stroke	637 (10%)	3831 (6%)	371 (8%)	2462 (6%)
Lung diseases				
Asthma	247 (4%)	1672 (3%)	165 (4%)	1167 (3%)
Chronic obstructive lung disease	466 (7%)	2756 (5%)	288 (7%)	1704 (4%)
Rheumatic diseases				
Rheumatoid arthritis	205 (3%)	1061 (2%)	100 (2%)	654 (2%)
Arthralgia	50 (1%)	163 (0%)	28 (1%)	117 (0%)
Arthritis	135 (2%)	692 (1%)	80 (2%)	474 (1%)

(Continues)

TABLE 1 (Continued)

	CC cases N = 6250	CC controls N = 59 842	LC cases N = 4402	LC controls N = 41 539
Spondyloarthritis	18 (0%)	102 (0%)	11 (0%)	75 (0%)
Skin diseases				
Atopic eczema	8 (0%)	104 (0%)	8 (0%)	73 (0%)
Psoriasis	73 (1%)	303 (1%)	53 (1%)	243 (1%)
Malignant melanoma	35 (1%)	403 (1%)	30 (1%)	259 (1%)
Nonmelanoma skin cancer	99 (2%)	1044 (2%)	68 (2%)	662 (2%)

CC, collagenous colitis; LC, lymphocytic colitis.

colitis (75%) compared to lymphocytic colitis (65%). The number of registered diagnoses was not significantly different between the cases and controls, except for hypothyroidism and vascular diseases, which were more predominant among cases. Compared with controls, cases demonstrated a higher usage of drugs in collagenous colitis compared to lymphocytic colitis for nearly all drug classes.

The proportion of cases and controls in each category that redeemed a prescription of PPI within 90 days prior to their index date are shown in Table 2. We found strong associations between current PPI use and both collagenous colitis (adjusted OR [aOR] (6.98; 95% CI: 6.45-7.55) and lymphocytic colitis (aOR 3.95; 95% CI: 3.60-4.33). This association was observed across all PPIs. Analyses for individual PPIs showed the strongest association with current use of lansoprazole for both collagenous colitis (aOR 15.74; 95% CI: 14.12-17.55) and lymphocytic colitis (aOR 6.87; 95% CI: 6.00-7.86). This pattern was confirmed using our sensitivity analysis, which excluded all subjects who had a history of use for more than one PPI (data not shown).

When considering timing, ORs were highest for current and recent use of PPI for both two subtypes of microscopic colitis, but the association was attenuated for both collagenous colitis and lymphocytic colitis when considering past exposure (Table 3). Among current users of PPI, we examined the effect of the cumulative amount prescribed 365 days before the index date as a proxy for daily intake. A comparison of 2470 cases of collagenous colitis and 1267 cases of lymphocytic colitis with current use of and without prescribed PPI showed no increased risk of microscopic colitis with increasing dose (Table 4). The combination of NSAID and PPI was more frequently prescribed in cases of microscopic colitis compared with controls, and the adjusted OR for collagenous colitis and lymphocytic colitis was 7.45 (95% CI: 6.63-8.38) and 3.54 (95% CI: 2.98-4.20), respectively (Table 5). However, enhanced OR with concomitant use of PPI and NSAID was not observed, as the OR was merely the sum of the two ORs.

We performed a post hoc analysis after observing a particularly high OR for lansoprazole. The OR for collagenous colitis of current users of lansoprazole compared with users of any other PPIs and lymphocytic colitis was 5.04 (95% CI: 4.31-5.90) and 2.38 (95% CI: 1.93-2.94), respectively (Table 6). To address a potential cohort effect, we analysed data separately for 2004-2008 and 2009-2013, finding no indication of a systematic difference for example, OR for any PPI and collagenous colitis: 9.06 (2004-2008) vs 9.24 (2009-2013) (Table S1). Analysis of drivers of the selection of lansoprazole over nonlansoprazole PPIs resulted in generally weak or moderate associations, in which the lowest and highest OR were 0.46 (atopic eczema) and 1.71 (colon cancer) (Table S2).

TABLE 2 Crude and adjusted odds ratios (OR) of collagenous and lymphocytic colitis by the current prescription of proton pump inhibitors

	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Collagenous colitis				
Never use of PPI	2040	40 533	1.00 (ref)	1.00 (ref)
Omeprazole	285	1528	4.23 (3.61-4.96)	3.14 (2.66-3.70)
Pantoprazole	359	1764	4.33 (3.75-5.00)	3.01 (2.58-3.50)
Lansoprazole	1712	1923	20.64 (18.59-22.92)	15.74 (14.12-17.55)
Esomeprazole	257	1020	5.22 (4.40-6.20)	3.75 (3.13-4.49)
Any PPI	2470	6088	9.17 (8.52-9.88)	6.98 (6.45-7.55)
Lymphocytic colitis				
Never use of PPI	1980	28760	1.00 (ref)	1.00 (ref)
Omeprazole	208	882	3.84 (3.20-4.61)	3.01 (2.49-3.63)
Pantoprazole	310	1166	3.97 (3.40-4.62)	2.60 (2.21-3.06)
Lansoprazole	659	1234	8.92 (7.84-10.15)	6.87 (6.00-7.86)
Esomeprazole	175	602	4.30 (3.52-5.24)	2.93 (2.37-3.62)
Any PPI	1267	3791	5.24 (4.80-5.72)	3.95 (3.60-4.33)

PPI, proton pump inhibitor; OR odds ratio, CI, confidence interval.
Adjusted for empirically identified confounders, that is, use of NSAIDs, any antidepressant, any antihypertensive, benzodiazepines and a past history of ischaemic heart disease or hypothyroidism.

TABLE 3 Use of proton pump inhibitors and risk of microscopic colitis by timing of use

	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Collagenous colitis				
Never users	2040	40 533	1.00 (Ref)	1.00 (Ref)
Current users	2470	6088	9.17 (8.52-9.88)	6.98 (6.45-7.55)
Recent users	904	3225	5.95 (5.39-6.57)	5.16 (4.66-5.72)
Past users	836	9996	1.75 (1.60-1.92)	1.52 (1.39-1.67)
Lymphocytic colitis				
Never users	1980	28760	1.00 (Ref)	1.00 (Ref)
Current users	1267	3791	5.24 (4.80-5.72)	3.95 (3.60-4.33)
Recent users	413	2102	2.82 (2.49-3.20)	2.31 (2.03-2.64)
Past users	742	6886	1.59 (1.45-1.75)	1.35 (1.23-1.49)

Never users had no recorded proton pump inhibitor prescriptions at any time before their index date. *Current users* were defined as having redeemed a prescription of proton pump inhibitor within 90 days prior to their index date. *Recent users* were defined as having redeemed at least one prescription of proton pump inhibitor in the period 91-365 days prior to their index date but not having redeemed any prescription for proton pump inhibitor within the last 90 days. *Past users* had their last prescription more than 365 days before their index date.
Adjusted for empirically identified confounders, that is, use of NSAIDs, any antidepressant, any antihypertensive, benzodiazepines and a past history of ischaemic heart disease or hypothyroidism.

TABLE 4 The amount of proton pump inhibitor prescribed for current users within the year before the index date and the risk of microscopic colitis. Recent and past users were excluded from this analysis

	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Collagenous colitis				
No prescriptions of PPIs	2876	50 529	1.00 (ref)	1.00 (ref)
0-180 DDD	1181	2030	10.83 (9.87-11.89)	8.91 (8.09-9.81)
181-365 DDD	800	2131	7.38 (6.66-8.18)	5.60 (5.04-6.24)
>365 DDD	489	1927	4.91 (4.35-5.53)	3.21 (2.82-3.64)
Lymphocytic colitis				
No prescriptions of PPIs	2722	35 646	1.00 (ref)	1.00 (ref)
0-180 DDD	623	1342	6.18 (5.53-6.91)	5.20 (4.63-5.84)
181-365 DDD	362	1284	3.83 (3.35-4.37)	2.88 (2.50-3.31)
>365 DDD	282	1165	3.14 (2.72-3.64)	2.02 (1.73-2.35)

PPI, proton pump inhibitor; DDD, defined daily dose; OR odds ratio, CI, confidence interval.
Adjusted for empirically identified confounders, that is, use of NSAIDs, any antidepressant, any antihypertensive, benzodiazepines and a past history of ischaemic heart disease or hypothyroidism.

TABLE 5 Current use of proton pump inhibitor and nonsteroidal anti-inflammatory drug alone or combined and the risk of microscopic colitis

	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Collagenous colitis				
Neither PPI nor NSAIDs	3157	48 037	1.00 (ref)	1.00 (ref)
PPI but not NSAIDs	1751	4856	6.00 (5.59-6.44)	4.78 (4.43-5.15)
NSAIDs but not PPI	623	5717	1.72 (1.56-1.89)	1.60 (1.45-1.76)
Both PPI and NSAIDs	719	1232	9.26 (8.26-10.36)	7.45 (6.63-8.38)
Lymphocytic colitis				
Neither PPI nor NSAIDs	2714	33 998	1.00 (ref)	1.00 (ref)
PPI but not NSAIDs	1006	3059	4.29 (3.94-4.68)	3.34 (3.05-3.66)
NSAIDs but not PPI	421	3750	1.41 (1.26-1.57)	1.28 (1.14-1.43)
Both PPI and NSAIDs	261	732	4.88 (4.15-5.75)	3.54 (2.98-4.20)

PPI, proton pump inhibitor; NSAID, nonsteroid anti-inflammatory drugs; DDD, defined daily dose; OR odds ratio; CI, confidence interval.

TABLE 6 Post hoc analysis of odds ratios of collagenous and lymphocytic colitis by the current prescription of lansoprazole vs other PPIs

	Numbers exposed			
	Cases	Controls	Crude OR (95% CI)	OR_adjusted (95% CI)
Collagenous colitis				
Nonlansoprazole PPI	758	4165	1.00 (ref)	1.00 (ref)
Lansoprazole	1712	1923	4.94 (4.24-5.76)	5.04 (4.31-5.90)
Lymphocytic colitis				
Nonlansoprazole PPI	608	2557	1.00 (ref)	1.00 (ref)
Lansoprazole	659	1234	2.26 (1.84-2.77)	2.38 (1.93-2.94)

PPI, proton pump inhibitor.
Adjusted for empirically identified confounders, that is, use of NSAIDs, any antidepressant, any antihypertensive, benzodiazepines and a past history of ischaemic heart disease or hypothyroidism.

4 | DISCUSSION

This population-based study presents data obtained from large cohorts of patients with microscopic colitis and confirms previous reports associating PPI with an excessive risk for microscopic colitis. Our main observation was an association between exposure to PPI and risk of microscopic colitis, which appeared to be highly

dependent on the selected PPI, with lansoprazole exhibiting the strongest association in cases of collagenous colitis. The remaining three PPIs were positively, but less strongly, associated with both collagenous colitis and lymphocytic colitis. Second, we demonstrated that the increased risk is primarily related to current and recent use of PPI; however, we did not identify any relationship with the total amount of drug used during the year before diagnosis. Furthermore, we observed no clear dose-response association. Indeed, there appeared to be a reverse association, with a lower risk associated with higher doses. However, this finding should not be taken too literally. Due to the lack of valid data on prescribed or actually taken daily doses, we used the cumulative quantity dispensed over the last year as a proxy for daily intake. It is highly conceivable that for an effect of ongoing treatment, the cumulative dose-response effect would be inverse. Patients who are at particular risk of developing the outcome do so early and stop their treatment, whereas patients who have tolerated it for some time are likely to continue tolerating it. Thereby, an inverse cumulative dose-response effect emerges.

4.1 | Strengths and limitations

The main strength of this study is its large sample size. To the best of our knowledge, this is the largest study in this field. The uniformly organised Danish health-care system permitted analyses of a nationwide cohort, thereby reducing the risk of selection bias. The Pathology Register was used by pathologists in the daily diagnostic process and covered all pathological data in Denmark. The reliability of the recorded diagnoses in the Pathology Register has not been validated. However, the diagnostic criteria for microscopic colitis were established in 1989,[19] and in a previous study, inter- and intraobserver agreement was very high for the diagnostic categories of microscopic colitis.[20] The information of drug exposure was obtained from a nationwide prescription database with prospective and electronic recording of redeemed prescriptions reducing the risk of recall bias and increasing the likelihood of valid registration of actual drug consumption.[16] Our study is unique due to its ability to compare different PPIs. Over-the-counter sales were not included in the analysis, but over-the-counter sale of PPI in Denmark is as low as 3%,[21] and we therefore considered both the account of PPI exposure and the recorded microscopic colitis diagnosis valid. Our study was register-based and therefore without access to information on the range of lifestyle factors that may have confounded the association between exposure to PPI and microscopic colitis, including smoking and alcohol use. The number of smokers among PPI users was higher than among nonusers, and smoking is also a known risk factor for microscopic colitis, which could affect the estimated OR.[1, 22] However, it appears unlikely that such potentially confounding factors would affect the selection of lansoprazole over other PPIs. The indications of the four PPIs are virtually identical, and we have no reason to believe that the selection of PPI was based on factors that were not accounted for. This was largely confirmed in our post hoc analysis of drivers of selection of lansoprazole over other PPIs, which failed to demonstrate any meaningful differences. Thus, a potential confounding factor would affect the association with all PPIs equally and does not explain the observed differences observed between PPIs. Moreover, analysing two different study periods did not disclose any time trend in OR.

PPIs are among the most widely used drugs to treat gastrointestinal tract disorders, such as gastro-oesophageal reflux diseases, gastroduodenal ulcers and gastroduodenitis. In this study, only a few cases had registered a relevant diagnosis for PPI treatment, which is consistent with previous studies demonstrating that PPIs are frequently prescribed for longer periods of time without evidence-based indication.[23] PPI users are overrepresented in groups with nonspecific gastrointestinal complaints. Thus, endoscopic workup is often initiated in patients receiving PPIs, which potentially results in a more frequent diagnosis of microscopic colitis in this group of patients. However, this finding is unlikely to completely explain the association. The PPI-microscopic colitis association was very strong in our study, and it was different for different categories of microscopic colitis and different PPIs. It is important to recognise that a substantial number of patients are diagnosed with microscopic colitis without any recorded exposure to PPI. In the present study, 46% of patients with collagenous colitis and 62% of patients with lymphocytic colitis had no recorded exposure to PPIs.

The pathophysiological explanation of PPI-associated microscopic colitis remains poorly understood. It is unlikely to be mediated solely by the acid-suppressing effect of PPIs. As all PPIs have the same intrinsic ability to suppress acid secretion, we did not expect a differential effect between different PPI entities.[24] Proton pumps are present in the colon mucosa, and it has been suggested that inhibition of these proton pumps could trigger an immune response, resulting in microscopic colitis.[25] Due to the different binding sites of PPIs to the proton pump and lansoprazole-binding cysteine residue 321, it has been hypothesised that lansoprazole induces specific changes in the colonic proton pump. The differences in OR between PPIs suggest that lansoprazole-related microscopic colitis is dependent on a chemical structure or property that is particularly pronounced for lansoprazole. It would have been interesting to study the effect of other acid-suppressing drugs, such as histamine-2-receptor antagonists. An apparent effect of these drugs on the microscopic colitis risk would indicate either confounding by indication or that the effect was mediated through acid suppression. Unfortunately, the sales of histamine-2-receptor antagonists have plummeted in recent years, making a study on these drugs uninterpretable.

We included cases of virtually all incident microscopic colitis patients diagnosed during the study period. Of these cases, 2470 collagenous colitis cases and 1267 lymphocytic colitis cases were current users of PPIs. Assuming that our adjusted OR estimates are valid estimates of a causal association and applying the equations for attributable proportions among those exposed (AP_{exp} = OR/(OR-1)),[18] it can be estimated that during the study period, 2105 cases of collagenous colitis and 969 cases of lymphocytic colitis were caused by PPI use. During the study period, the total sale of PPI was 823 million DDD in Denmark.[26] Thus, the risk is equivalent to one excess case of collagenous colitis per 390 000 DDDs of PPI consumed and one excess case of lymphocytic colitis per 850 000 DDDs. Although

the association between PPIs and microscopic colitis is strong for both entities, the risk for individual PPI users is fairly low.

In conclusion, we found a strong association between current PPI use and microscopic colitis, especially for lansoprazole. However, the potential roles of PPI exposure in the development of collagenous colitis and development of lymphocytic colitis should be further explored. It is currently unknown whether PPI-induced microscopic colitis is reversible. The finding of a substantially weaker association with previous use of PPI in our study suggests that this might be the case, although this finding should be confirmed in a more focused study. Studies on the effect of drug discontinuation and rechallenge of clinical symptoms and colonic histology may help to clarify this issue. There is currently insufficient evidence to recommend specific strategies for PPI use in patients with microscopic colitis. As always, an inappropriately prescribed PPI should be discontinued.

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AUTHORSHIP

Guarantor of the article: Dr. Bonderup.

Author contributions: OKB, GLN, MD and JH involved in the conception and design of the study; OKB, GLN, AP and JH analysed and interpreted the data; OKB drafted the manuscript; OKB, GLN, MD, AP and JH involved in critical revision of the manuscript; AP and JH analysed statistical data.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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