ORIGINAL ARTICLE

The association between the intake of specific dietary components and lifestyle factors and microscopic colitis

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BACKGROUND/OBJECTIVES: The incidence of microscopic colitis (MC) has increased over the previous decades. In addition to smoking and drugs, currently unidentified environmental factors may have a role. The aim of this study was to determine whether specific dietary or other lifestyle factors were associated with the development of MC.
SUBJECT/METHODS: The population-based cohort Malmö Diet and Cancer Study of 28 095 individuals was examined. Information about dietary habits was collected by a modified diet history method. Data on anthropometry were measured, and socio-economic and lifestyle factors were collected by questionnaires. Cases of MC were identified in medical registers. Associations were estimated using Cox regression analysis.
RESULTS: During a 22-year period, 135 patients were diagnosed with MC. Intakes of protein, carbohydrates, sucrose, saturated fat, monounsaturated fat, polyunsaturated fat, omega-3 or omega-6 fatty acids, fibre and zinc were not associated with MC. We could verify the previously reported association between MC and smoking (hazard ratio (HR): 2.29; 95% confidence interval (CI): 1.66–3.84) and the female gender (HR: 3.57; 95% CI: 2.22–5.74). High alcohol consumption was associated with an increased risk for MC (HR: 1.89 for the highest quartile; 95% CI: 0.82–4.33, P for trend = 0.032). In a *post hoc* analysis, alcohol intake including all patients independently of consumption seemed to reduce the smoking-related risk.
CONCLUSIONS: Despite a large cohort and a long follow-up period, we could not detect any dietary risk factors for MC. The aetiological mechanisms behind the positive impact of smoking and alcohol on MC risk should be investigated.

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INTRODUCTION

Microscopic colitis (MC) is an inflammatory disorder in the colonic mucosa that causes chronic, non-bloody diarrhoea. Because of histopathological differences, MC is divided into two subtypes: collagenous colitis (CC) and lymphocytic colitis (LC).[1] Age, female gender, smoking and drugs are known risk factors for the development of MC.[2–6] Data on alcohol consumption are not conclusive, but a possible association could exist.[4,7]

In accordance with the classic inflammatory bowel diseases (IBDs), ulcerative colitis (UC) and Crohn's disease (CD), the global incidence of both CC and LC has increased during the last decades.[1,8,9] An increased awareness of the disease improved diagnostic procedures, and yet unidentified environmental factors could contribute to this change.

MC has many features in common with classic IBD. Environmental factors, for example, certain dietary factors, smoking and alcohol have been suggested to have a role in IBD. There is a lack of investigations on the impact of dietary factors on the occurrence of MC. To anticipate the possible effect of dietary factors on MC, one possibility is to look at the observations made in IBD. A high intake of n-6 polyunsaturated fatty acids, which are found in red meat and margarine, increases the risk for developing both UC and CD.[10–12] A high total intake of fat also seems to result in an increased risk for IBD.[11] In contrast, fish consumption, particularly fish containing high concentrations of n-3 polyunsaturated fatty acids, seems to be negatively associated with UC and

CD in some studies,[10,12,13] whereas another study found a positive association between omega-3 and CD.[11] High consumption of fibre and fruit has been associated with a decreased risk of developing CD,[11] and high vegetable intake was associated with a decreased risk of developing UC.[14]

Increased carbohydrate intake, as well as increased intake of plant polysaccharides (fibres), influences bacterial metabolism in the large intestine.[15,16] The gut microbiota could protect us from pathogens and is believed to influence gut inflammation through several different mechanisms.[10,11]

Some minerals influence the immune response. Zinc has been suggested to have a great impact on immune function in general,[17] and a lower concentration of zinc in the drinking water increases the risk of type 1 diabetes.[18] Zinc deficiency has been shown to increase symptoms in an experimental colitis model in rats.[19]

There is a known association between MC and coeliac disease.[20] The immune response in the gut in MC is dominated by a Th1 mucosal cytokine profile, which is in many ways similar to that in coeliac disease, suggesting a response to luminal antigens in MC.[21]

Our hypothesis was that lifestyle factors such as dietary factors, smoking, alcohol, obesity, education and physical activity are involved in the development of MC. To address this, the influence of lifestyle factors on incident MC was studied in a population-based cohort of 28 095 participants.[22–24] The aim of this

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prospective study was to examine whether lifestyle factors were associated with the development of MC.

MATERIALS AND METHODS

Study population

The Malmö Diet and Cancer (MDC) study is set in Malmö, Sweden's third largest city. The population was identified through the Swedish National Population Registry. All men born between 1923 and 1945 and all women born between 1923 and 1950 living in Malmö during the screening period (1991–1996) were invited to participate. Recruitment was conducted through advertisements in the local media and through invitation by mail. The only exclusion criteria were inadequate Swedish language skills or mental incapacity.

A total number of 74 138 inhabitants were invited to participate. With a participation rate of ~ 40%, the final cohort consisted of 28 098 individuals. A comparison of participants and non-participants has been previously presented.[22,23] In the present study, we excluded all participants with prevalent MC (n = 3). This left 28 095 study subjects available for analysis. Of these, 11 062 were men (39%) and 17 033 were women (61%), with a mean age of 58 years (range 44–74). A more detailed description of the cohort is described elsewhere.[23,24]

Data collection

The participants visited the MDC centre twice. During the first visit, the study objects obtained information about the background and aim of the project and detailed instructions about the dietary assessment and other procedures of the study, and received an extensive lifestyle questionnaire to complete at home (including education, socio-economic variables, reproduction, alcohol habits, smoking, physical activity, household activity, substantial dietary change and medical history). The season of the data collection was registered. Height, weight and blood pressure were measured. At the second visit, a dietary interview was performed by trained interviewers, and the lifestyle questionnaire was checked for incomplete answers.

Diet assessment methodology

The dietary assessment method, specifically developed for the MDC study,[25,26] collected information on dietary intake by using a combination of the following:

A 7-day food diary where information about lunch and dinner meals, cold beverages including alcohol, pharmaceutical drugs, natural medication and nutrient supplements was registered.
A 168-item dietary questionnaire for the assessment of foods not covered in the 7-day food diary consumed during the last year, including information about portion size (assessed using photographic aids) and frequencies. The participants also described the overall meal pattern during weekdays and weekends.
A 1-h-long interview where participants were asked questions about portion size (assessed using photographic aids), food choices and food preparation practises for the foods collected in the food diary. The interviewer checked the food diary and dietary questionnaire so that the reported food consumption did not overlap and was in concordance with the reported meal pattern by the participant.

The average daily intake of foods (grams per day) was calculated based on the frequency and portion size estimates from the questionnaire and food diary (and interview). The food intake was converted to nutrient data using the MDC food and nutrient database, originating from PC KOST2-93 of the Swedish National Food Administration.[25] Data on the relative validity and reproducibility for the diet method have been described in detail.[23,26,27] Energy-adjusted validity correlations were as follows: protein, 0.54/0.53; carbohydrates, 0.66/0.70; fat, 0.64 (men)/0.69 (women); and fibre, 0.74/0.69. In September 1994, the routines for the coding dietary data were slightly altered to reduce the interview time.[25] A method version variable was created to control for undue influences.

Dietary factors

The dietary factors examined in this study were the average daily intakes from foods and supplements: protein, carbohydrates, total fat, saturated fatty acids (SFAs), monounsaturated fatty acids, polyunsaturated fatty acids (PUFAs), n-3 PUFA, n-6 PUFA, dietary fibre and zinc. All factors were adjusted for total energy intake, that is, energy percentage (E%) for macronutrients, g/MJ for fibre and mg/MJ for zinc.

We also used a diet quality index score developed within the MDC study to reflect the adherence to current Swedish nutrition recommendations and dietary guidelines.[28] The participants were given one point for reaching the recommended intake level for each of the following six dietary factors: SFAs (⩽14 E%), PUFAs (5–10 E%), sucrose (⩽10 E%), fibre (⩾2.4 g/MJ), fruits and vegetables (⩾400 g/day), and fish and shellfish (⩾300 g/week). The cutoff for SFAs was increased to 14 E% (that is, approximately one standard deviation (s.d.) increase) because few of the participants had an intake below the recommended level (10 E%). The score was divided into three categories: low (0–1 points), medium (2–4 points) and high (5–6 points).

Other variables

Smoking was categorized into never smokers, ex-smokers and smokers. Alcohol habits were categorized into five categories. Zero consumers reported no consumption during the past year in the questionnaire and no consumption in the 7-day food diary. The other individuals were divided into gender-specific quartiles based on their consumption in the food diary. Body mass index (BMI) was categorized into quartiles. The education level was divided into elementary school or below, primary and secondary school, upper secondary school, further education without a degree and university degree. Leisure-time physical activity was obtained from the estimated minutes per week spent on 17 different activities. A score was constructed taking into account the intensity and duration of the activity; the score was divided into quartiles.[29]

Definition of MC

The diagnosis of MC is based on the presence of gastrointestinal symptoms in combination with a macroscopic normal endoscopy and microscopic inflammation. The established histopathological criteria for CC are (i) a chronic inflammatory infiltrate in the lamina propria with (ii) a thickened subepithelial collagen layer ⩾ 10 μm and (iii) epithelial damage such as flattening and detachment. To fulfil the criteria for LC, an intraepithelial lymphocyte count ⩾ 20 per 100 surface epithelial cells must also be present.[30]

Cases

Patients who had undergone colonoscopies through the end of 2013 in Malmö owing to the occurrence of chronic gastrointestinal symptoms, in which the histopathological criteria for MC were fulfilled according to gastrointestinal pathologists with a special interest in and knowledge of MC,[30] were initially selected for this study. Only those who were included in the MDC study before disease development were finally included. The diagnosis of MC was set by the physician in charge, and all medical registers were scrutinised to confirm the diagnosis.

Statistical analyses

Patients with MC were compared with non-cases within the total cohort. The associations between dietary factors (divided into quartiles with the first quartile used as the reference) and lifestyle factors and MC risk were estimated through the Cox proportional-hazards regression models with time from baseline until diagnosis, death or end of follow-up as the underlying time variable. The analyses were adjusted for potential confounding factors (age, gender and smoking habits). Analyses with dietary factors were also adjusted for total energy intake, season for inclusion in the study and version of the dietary method. We also tested P for trend, that is, the linear association between lifestyle and dietary factors and MC risk by using these variables as continuous variables (for example, 1–4 for the dietary factors). This analysis tested whether increasing amounts of exposure had a positive or a negative association with MC risk. All dietary parameters were also tested in a multiple logistic regression model but with the same non-significant outcome (data not shown). In a sensitivity analysis, we excluded individuals with a reported dietary change in the past.[31,32] In the calculation of the association between smoking, alcohol and MC risk, both smoking and alcohol intake were set as reference. Values are given as hazard ratios (HRs) and 95% confidence interval (CI) or mean and range. A P-value below 0.05 was considered

statistically significant. For all statistical analyses, SPSS Version 22 (IBM Corp., Armonk, NY, USA) was used.

Ethics

The Ethics Committee at Lund University approved the design of the original MDC study protocol, which complied with the Declaration of Helsinki (LU-51-90). The study protocol for the present investigation was approved separately (LU 650/13).

RESULTS

In the total cohort, 135 patients with incident MC were identified during the follow-up period of 22 years. Of these, 115 were women (85%) with a mean age of 58 years (range 45–73), and 20 were men (15%) with a mean age of 61 years (range 49–73). Females had a higher risk of developing MC compared with men (HR 3.57; 95% CI 2.22–5.74; $P < 0.001$). Of the 135 patients with MC, 73 had CC (54%) and of these, 63 were women and 10 were men with a mean age of 57 years (range 46–73). Further, 62 had LC (46%) and of these, 52 were women and 10 were men with a mean age of 59 years (range 45–73). Baseline characteristics at the

time for screening are given in Table 1. The age at the time of screening did not differ between cases and non-cases (HR 1.02; 95% 0.99–1.04; $P = 0.19$). The mean age at MC diagnosis was 69 years (range 49–86) for women and 72 years (range 52–85) for men.

The mean intake of different dietary factors separated into cases and non-cases is shown in Table 2. Neither the intake of protein, carbohydrates, sucrose and fat, including SFA, monounsaturated fatty acid and PUFA, nor that of fibre or zinc was associated with risk for MC (Table 3). Subgroup analysis of patients with CC and LC did not reveal any significant differences between cases and non-cases (data not shown). Furthermore, a diet quality index score based on adherence to the recommended intake of SFAs, PUFAs, sucrose, fibre, fruit and vegetables, and fish and shellfish was applied to determine whether a food pattern was associated with risk. No statistically significant associations could be found (Table 4). In a sensitivity analysis, those that had changed their dietary habits were excluded. This procedure did not influence the results (data not shown).

Lifestyle factors are depicted in Table 5. There was a strong association between smoking and MC risk (P for trend < 0.001).

Table 1. Baseline characteristics for the studied population

	Non-cases N = 27 960		Cases N = 135	
Gender (n, %)				
Males	11 042	39.5	20	14.8
Females	16 918	60.5	115	85.2
Mean age (years) (range)	58.1	(44.5–73.6)	58.2	(44.9–72.8)
Median age (years) (IQR)	57.8	(51.3–64.2)	58.2	(51.3–64.0)
Smoking habits (n, %)				
Never smokers	10 605	37.9	39	28.9
Ex-smokers	9465	33.9	41	30.4
Smokers	7878	28.2	55	40.7
Sum	27 948		135	
Alcohol habits (g/day) (n, %)				
Zero consumers	1806	6.5	7	5.2
⩽ 2.55	6585	23.6	33	24.4
2.55–7.93	6499	23.2	24	17.8
7.93–15.97	6533	23.4	38	28.1
15.98–194	6537	23.4	33	24.4
Sum	27 960		135	
BMI (kg/m^2) (n, %)				
⩽ 23.01	6999	25.0	37	27.4
23.02–25.28	7020	25.1	37	27.4
25.29–27.97	6932	24.8	32	23.7
⩾ 27.98	7004	25.1	29	21.5
Sum	27 955		135	
Education				
Elementary school or below	11 720	42.0	57	42.2
Primary and secondary school	7300	26.2	32	23.7
Upper secondary school	2472	8.9	17	12.6
Further without degree	2427	8.7	15	11.1
University degree	3970	14.2	14	10.4
Sum	27 889		135	
Physical activity (points) (n, %)				
⩽ 3950	6943	25.0	31	23.0
3951–6750	6942	25.0	40	29.6
6751–10 670	6941	25.0	34	25.2
⩾ 10 671	6943	25.0	30	22.2
Sum	27 769		135	

Abbreviations: BMI, body mass index; IQR, interquartile range. Leisure-time physical activity was obtained from the estimated minutes per week spent on 17 different activities. A score was constructed taking into account the intensity and duration of the activity; the score was divided into quartiles.

Table 2. Dietary intake among non-cases and microscopic colitis patients

| | Non-cases N = 27 960 | | Cases N = 135 | |
	Mean	Range	Mean	Range
Protein (E%)	15.7	6.3–30.9	15.9	9.3–24.8
Carbohydrates (E%)	44.9	16.1–76.0	45.2	32.3–57.3
Fat (E%)	37.6	4.3–69.8	37.0	23.6–54.1
Saturated fatty acids (E%)	16.2	0.8–38.3	16.1	8.5–29.2
Monounsaturated fatty acids (E%)	13.1	0.5–26.2	12.7	6.6–18.2
Polyunsaturated fatty acids (E%)	6.0	1.7–24.8	5.9	3.0–10.9
Omega-3 (E%)	1.0	0.2–4.8	1.0	0.4–2.3
Omega-6 (E%)	4.8	0.7–24.4	4.7	2.4–9.1
Fibre (mg/MJ)	2.2	0.5–8.0	2.2	1.0–4.4
Zinc (mg/MJ)	1.4	0.5–26.8	1.6	0.7–21.0
Zinc (mg)	12.9	1.9–158.2	12.8	5.8–95.6

Abbreviations: E% = Energy percent. Range = min–max.

Increased alcohol intake was associated with an increased risk of developing MC (P for trend = 0.032). BMI, physical activity and education level did not differ between cases and non-cases.

A post hoc analysis was performed where the risk for MC was estimated by taking both alcohol (non-drinkers/drinkers) and smoking habits (non-smokers/current smokers) into account. Among non-drinkers/non-smokers 5 cases/100 000 person-years were observed compared with 83 cases/100 000 person-years among non-drinkers/smokers and 42 cases/100 100 person-years among drinkers/smokers. Compared with drinkers/smokers, a reduced risk for MC could be seen in both non-drinkers/non-smokers and drinkers/non-smokers. In non-drinkers/smokers, an increased risk was observed, although not statistically significant (Table 6).

DISCUSSION

The results in this study could not verify the hypothesis that intake of certain dietary factors that is, protein, carbohydrates, sucrose, fat, SFAs, monounsaturated fatty acids, PUFAs, n-3 PUFA, n-6 PUFA, fibre or zinc should be significant risk factors for the development of MC. A diet quality index based on adherence to dietary recommendations failed to reveal any differences between cases and non-cases. We could, however, verify the previously reported association between MC and smoking and the female gender. High alcohol consumption seemed to be associated with an increased risk for MC. However, in a post hoc analysis, alcohol intake per se seemed to—at least to some degree—reduce the increased smoke-related risk. In contrast, BMI, education or physical activity was not associated with any significant risk for the development of MC.

To the best of our knowledge, this is the first prospective study on the impact of dietary factors and lifestyle factors on the occurrence of MC. The principal strength of this study is the prospective design where pre-illness assessment and registration of dietary intake before disease onset data were performed. Because diagnosis of the disease may introduce dietary changes, prospective information of dietary habits may limit the influence of recall bias. In addition, the methodology of dietary assessment has a relatively high validity.[27,33] In view of the long time span, there is a possibility that the participants may have changed their dietary habits during follow-up. Especially in the Western world, the use of prepacked, salted and processed food has increased substantially over the last decades—based on the population level.[34] However, a sensitivity analysis failed to show any

alterations. Onset of a significant disease such as cardiovascular disease may also influence a person's preferences in a healthier direction.[35] Of course, the long time span between interview and disease onset is a limitation. This is, however, an obstacle that is apparent in most large epidemiological population-based studies. For example, the investigation on 203 193 European individuals with a maximum follow-up time of 11 years from which 126 people with UC could be identified is based on single food recordings.[12] However, studies with repeated measurements—based on the individual level—indicate that most people tend to stick to their meal choices over time.[36,37] Furthermore, any changes in meal preferences over time should have an impact on both patients and non-cases. The cohort consisted of a large number of individuals, almost 30 000, who also had an age profile similar to the typical MC patient. Because follow-up occurred during a long time span (between 17 and 22 years; inclusion period 1991–1996 with follow-up until 2013), a fairly high number of people developing MC (n = 135) could be identified. On the basis of data from the same region on patients with CC, the incidence rate during the years 2001–2010 is known ($5.4/10^5$ inhabitants and year).[38] The age-adjusted number of patients who could be expected to develop CC during that decade was 35, which is the same number of patients who were identified in the present investigation. Although this estimation is restricted to only CC and not LC, and not the whole period, it gives an indication that the present investigation included a fairly representative disease population. Some limitations still have to be considered. Of all those invited to participate (74 138 inhabitants), only ~40% accepted the invitation (that is, 28 098 individuals). However, it is still regarded to be a fairly representative cohort.[22,23]

In a review article comprising 41 reports on diet in IBD, some correlations were reported. High intake of sugar and low intake of fruits and/or vegetables were associated with both CD and UC, whereas no definitive conclusions could be drawn for the intake of protein or unsaturated fatty acids.[39] Seven articles noted that a high sugar intake and five articles noted that a low fruit and/or vegetable intake were associated with UC. In a multicentre study comprising 126 UC patients, including four matched controls from a total cohort of 203 193 individuals, a significant association with intake of linoleic acid (an essential n-6 PUFA; odds ratio 2.49 for the highest quartile; 95% CI 1.23–5.07, P for trend = 0.02) was noted.[12] Despite the fact that these articles all found associations with diet and comprise a comparable number of patients, we could not find any statistically verified association in the present cohort. Consequently, diet probably influences MC to a lesser extent than classic IBD.

High alcohol intake seems to have a positive impact on the risk for MC. This is in line with a prospective cohort study on UC from United Kingdom (UK), where high intake of alcohol was associated with an increased risk for disease activity, whereas medium intake did not confer any risk.[40] In a Japanese case–control study, alcohol intake had a protective effect against UC compared with no alcohol intake.[41] The mechanisms behind these somewhat contradictory associations are unclear. As the reports come from different parts of the world, several confounding factors could contribute to this discrepancy. However, colitis, at least in mice, can be triggered by alcohol.[42] Ethanol and its metabolite acetaldehyde have several effects on the gastrointestinal tract. In particular, an observed increase in the permeability both in the small and large intestine is worth mentioning. Activation of cell signalling pathways, oxidative stress, remodelling of the cytoskeleton and modulation of the microbiota have been suggested as possible mechanisms.[43] Increased permeability is associated with several gastrointestinal diseases, and this effect may very well contribute to the disease course in MC as well.

In addition to alcohol, certain additives in spirits may also have a role. In the article from UK,[40] the authors speculate that—besides alcohol—sulphur and sulphate might also have a role, as

Table 3. Risk estimates for the intake of different dietary factors and microscopic colitis

Quartiles	Quartile range	Crude HR	95% CI	Adjusted HR	95% CI
Protein (E%)					
1	⩽ 14.01	1.00		1.00	
2	14.02–15.53	1.24	(0.76–2.04)	1.22	(0.74–2.00)
3	15.54–17.20	1.31	(0.80–2.14)	1.23	(0.75–2.03)
4	⩾ 17.21	1.25	(0.76–2.06)	1.26	(0.69–1.88)
P for trend		0.372		0.641	
Carbohydrates (E%)					
1	⩽ 41.11	1.00		1.00	
2	41.12–44.90	0.85	(0.52–1.38)	0.87	(0.53–1.41)
3	44.91–48.66	0.87	(0.54–1.41)	0.89	(0.55–1.45)
4	⩾ 48.67	1.09	(0.69–1.71)	1.14	(0.72–1.81)
P for trend		0.700		0.565	
Sucrose (E%)					
1	⩽ 6.08	1.00		1.00	
2	6.09–8.04	0.87	(0.53–1.44)	0.81	(0.49–1.35)
3	8.05–10.34	1.12	(0.70–1.80)	1.03	(0.63–1.66)
4	⩾ 10.35	1.17	(0.73–1.87)	1.06	(0.65–1.71)
P for trend		0.345		0.782	
Fat (E%)					
1	⩽ 33.56	1.00		1.00	
2	33.57–37.54	0.75	(0.47–1.20)	0.75	(0.47–1.20)
3	37.55–41.57	0.80	(0.50–1.27)	0.80	(0.50–1.28)
4	⩾ 41.58	0.82	(0.52–1.30)	0.82	(0.51–1.30)
P for trend		0.433		0.454	
Saturated fatty acids (E%)					
1	⩽ 13.59	1.00		1.00	
2	13.60–15.73	0.86	(0.54–1.38)	0.82	(0.51–1.32)
3	15.74–18.32	0.90	(0.56–1.43)	0.83	(0.52–1.33)
4	⩾ 18.33	0.90	(0.56–1.40)	0.80	(0.50–1.29)
P for trend		0.699		0.394	
Monounsaturated fatty acids (E%)					
1	⩽ 11.64	1.00		1.00	
2	11.65–13.09	0.78	(0.49–1.24)	0.77	(0.48–1.23)
3	13.10–14.53	0.87	(0.55–1.37)	0.89	(0.56–1.40)
4	⩾ 14.54	0.71	(0.44–1.15)	0.75	(0.46–1.22)
P for trend		0.232		0.346	
Polyunsaturated fatty acids (E%)					
1	⩽ 4.85	1.00		1.00	
2	4.86–5.77	0.98	(0.61–1.55)	1.05	(0.66–1.66)
3	5.78–6.83	0.82	(0.51–1.32)	0.93	(0.57–1.50)
4	⩾ 6.84	0,85	(0.53–1.36)	1.00	(0.62–1.63)
P for trend		0.380		0.899	
Omega-3 (E%)					
1	⩽ 0.77	1.00		1.00	
2	0.78–0.92	0.71	(0.44–1.14)	0.70	(0.44–1.13)
3	0.93–1.12	0.71	(0.44–1.15)	0.71	(0.44–1.15)
4	⩾ 1.13	0.90	(0.58–1.41)	0.89	(0.57–1.41)
P for trend		0.630		0.625	
Omega-6 (E%)					
1	⩽ 3.80	1.00		1.00	
2	3.81–4.63	0.89	(0.56–1.40)	0.85	(0.61–1.51)
3	4.64–5.60	0.74	(0.46–1.19)	0.84	(0.52–1.34)
4	⩾ 5.61	0.69	(0.43–1.11)	0.84	(0.51–1.36)
P for trend		0.091		0.383	
Fibre (mg/MJ)					
1	⩽ 1.78	1.00		1.00	
2	1.79–2.15	1.36	(0.85–2.17)	1.32	(0.82–2.11)
3	2.16–2.59	0.79	(0.47–1.34)	0.74	(0.44–1.27)
4	⩾ 2.60	1.04	(0.64–1.69)	0.93	(0.57–1.54)
P for trend		0.573		0.320	

Table 3. (Continued)

Quartiles	Quartile range	Crude HR	95% CI	Adjusted HR	95% CI
Zinc (mg/MJ)					
1	⩽ 1.11	1.00		1.00	
2	1.12–1.25	0.77	(0.46–1.28)	0.80	(0.48–1.34)
3	1.26–1.45	1.12	(0.71–1.78)	1.19	(0.75–1.90)
4	⩾ 1.46	1.07	(0.67–1.71)	1.01	(0.66–1.68)
P for trend		0.455		0.493	
Total zinc[a] *(mg)*					
1	⩽ 9.18	1.00		1.00	
2	9.19–11.37	1.10	(0.71–1.71)	1.30	(0.83–2.03)
3	11.38–14.70	0.65	(0.40–1.08)	0.98	(0.59–1.64)
4	⩾ 14.71	0.75	(0.46–1.21)	1.12	(0.68–1.82)
P for trend		0.074		0.912	

Abbreviations: CI, confidence interval; E% = Energy percent; HR, hazard ratio. The HR was estimated through Cox proportional-hazards regression models with corresponding 95% CIs. HR (95% CI) is stated for quartiles of intake. Variables were adjusted for age, sex, smoking, season and method version. *N* cases: 135; *N* non-cases: 27 960. A general linear model was used to calculate *P* for trend. The quartiles were used as continuous variables. [a]Including supplementary zinc intake.

Table 4. Risk estimates for the intake of different foods based on a diet score

Diet index	Non-cases (n)	Cases (n)	Crude HR	95% CI	Adjusted HR	95% CI
Diet score						
0	815	8	1.00		1.00	
1	3455	16	0.47	(0.20–1.10)	0.52	(0.22–1.21)
2	7433	35	0.46	(0.21–1.00)	0.56	(0.26–1.20)
3	7553	33	0.42	(0.19–0.90)	0.52	(0.24–1.12)
4	4952	25	0.46	(0.21–1.01)	0.56	(0.25–1.26)
5	2794	11	0.35	(0.14–0.87)	0.43	(0.17–1.07)
6	958	7	0.61	(0.22–1.67)	0.76	(0.27–2.11)
Sum	27 960	135				
P for trend			0.32		0.59	

Abbreviations: CI, confidence interval; HR, hazard ratio. The HR was estimated through Cox proportional-hazards regression models with corresponding 95% CIs. HR (95% CI) is stated for a diet index based on the intake of saturated fat, polyunsaturated fat, sucrose, fibre, vegetables and fruit and fish, where each variable is given a score of 0 or 1. On the basis of these parameters, the group has been divided into six categories, where 0 is the unhealthiest and 6 is the healthiest food pattern. Variables were adjusted for age, sex, smoking, season and method version. A general linear model was used to calculate *P* for trend. The diet index scores were used as continuous variables.

many alcoholic drinks contain large amounts of sulphates. Sulphites are used as preservatives in beer, white and red wine (especially in bag-in-box wines) and soft drinks, which were all found to be related to increased disease severity in UC. Sulphite degrades thiamine, and foods high in thiamine (which is required by the probiotic bacteria lactobacilli) are reported to be associated with clinical improvement in UC. Furthermore, sulphide (that is derived from sulphite) is toxic to colonocytes.[44] However, it was not within the scope of the present investigation to explore the impact of different types of alcohol.

Non-drinkers/non-smokers had the lowest MC risk compared with drinkers/smokers. Smokers who did not consume alcohol had the highest risk, higher than in smokers/drinkers, although not significant. In an investigation in UC, a protective effect by a moderate alcohol intake disappeared when adjusted for smoking.[45] Despite the association between high alcohol intake and MC risk, alcohol intake *per se* in non-smokers was associated with a risk reduction compared with drinkers/smokers. This somewhat puzzling outcome has been observed in another study as well.[4] The contradictory results may depend on the fact that all alcohol consumers were put together in one group in the *post hoc* analysis. As the number of high consumers was fewer compared

with the number of low/medium consumers, the harmful effect of high alcohol volumes was hidden. A protective effect by alcohol against disease onset has previously been described for rheumatoid arthritis and multiple sclerosis.[46,47] The unifying factor in MC and multiple sclerosis is that the risk by smoking was reduced by alcohol, regardless of the initial alcohol-related risk level. The mechanisms underlying this phenomenon are unclear.

BMI, education level and physical activity were not associated with any risk increase for MC. BMI is associated with several immune-mediated diseases. According to a large Danish study based on 75 000 women followed for 11 years, there is a relationship between BMI and CD but not with UC.[48] Consequently, the relationship that seems to exist between obesity-mediated inflammation (based on the amount of visceral fat tissue) and CD[49] has not been proven in MC. High education seems to protect from CD[50] and rheumatoid arthritis,[51] indicating that socio-economic factors may have an impact on the risk at least in some other immune-mediated diseases. Physical activity has anti-inflammatory effects.[52] In view of this phenomenon, a reduced risk for MC in exercising individuals could hypothetically be expected. However, this was not the case in the present cohort. In other words, these lifestyle-related factors, which directly or

Table 5. Lifestyle factors in microscopic colitis

	Quartile range	Crude HR	95% CI	Adjusted HR	95% CI
Smoking					
Never smokers		1.00		1.00	
Ex-smokers		1.24	(0.80–1.92)	1.61	(1.03–2.51)
Smokers		2.10	(1.39–3.16)	2.53	(1.66–3.84)
P for trend		< 0.001		< 0.001	
Alcohol habits (g/day)					
Zero consumers		1.00		1.00	
Q1	⩽ 2.55	1.22	(0.54–2.76)	1.27	(0.56–2.88)
Q2	2.55–7.93	0.88	(0.38–2.04)	0.95	(0.41–2.22)
Q3	7.93–15.97	1.36	(0.61–3.05)	1.62	(0.72–3.65)
Q4	15.98–194	1.21	(0.54–2.75)	1.89	(0.82–4.33)
P for trend		0.522		0.032	
BMI (kg/m²)					
Q1	⩽ 23.01	1.00		1.00	
Q2	23.02–25.28	0.99	(0.62–1.56)	1.1	(0.70–1.74)
Q3	25.29–27.97	0.89	(0.55–1.43)	1.1	(0.66–1.73)
Q4	⩾ 27.98	0.83	(0.51–1.35)	0.94	(0.57–1.53)
P for trend		0.395		0.903	
Education					
Elementary school or below		1.00		1.00	
Primary and secondary school		0.87	(0.56–1.34)	0.83	(0.54–1.28)
Upper secondary school		1.37	(0.80–2.36)	1.77	(1.02–3.08)
Further without degree		1.26	(0.71–2.22)	1.41	(0.79–2.50)
University degree		0.70	(0.39–1.26)	0.80	(0.44–1.45)
P for trend		0.709		0.776	
Physical activity (points)					
Q1	⩽ 3950	1.00		1.00	
Q2	3951–6750	1.24	(0.78–1.99)	1.28	(0.80–2.04)
Q3	6751–10 670	1.06	(0.65–1.72)	1.10	(0.67–1.79)
Q4	⩾ 10 671	0.96	(0.58–1.59)	1.01	(0.61–1.66)
P for trend		0.706		0.852	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio. The HR was estimated through Cox proportional-hazards regression models with corresponding 95% CIs. HR was adjusted for sex, age and smoking, except for smoking that was adjusted for sex and age. A general linear model was used to calculate *P* for trend. Physical activity was obtained from estimated minutes per week spent on different activities. A score was constructed taking into account the intensity and duration of the activity; the score was divided into quartiles (Q). For smoking, 15 are missing in non-cases, and in education, 74 are missing in non-cases.

Table 6. Associations between intake of alcohol and/or smoking and microscopic colitis

Alcohol	Smoking	n	Cases (n)	Cases/10⁵ years	Crude HR	95% CI	Adjusted HR	95% CI
−	−	1307	1	4.8	0.11	(0.02–0.83)	0.09	(0.01–0.63)
+	−	18 843	79	25.4	0.59	(0.41–0.84)	0.55	(0.38–0.79)
−	+	501	6	83.3	2.07	(0.89–4.84)	1.65	(0.71–3.87)
+	+	7432	49	41.9	1.00	(ref)	1.00	(ref)

Abbreviations: CI, confidence interval; HR, hazard ratio. − denotes no intake of alcohol the last year or no current smoking; + denotes intake of alcohol the last year or current smoking. The HR was estimated through Cox proportional-hazards regression models with corresponding 95% CIs. HR was adjusted for sex and age. Cases/10⁵ years denotes the number of cases in that group (both non-cases and cases) divided by the total amount of person-years/100 000 years.

indirectly may influence inflammatory responses, did not associate with MC. Consequently, factors influencing the risk for MC probably have to be sought elsewhere.

The chosen dietary factors were selected based on previous data on other gastrointestinal diseases with an immune-mediated mechanism. Although the diet quality score did not reveal any significant association, a combined effect or other environmental factors cannot be ruled out. Food additives could be one such possibility,[53] as, for example, the addition of microbial transglutaminase in food makes gluten more immunogenic.[54]

This increased immune stimulus could hypothetically facilitate the development of coeliac disease and MC. An altered microbiota has also been observed in MC with a decreased number of *Akkermansia*, involved in mucin regulation,[55] and artificial sweeteners are deranging the microbiota, leading to disrupted glucose homoeostasis.[56] Another possible factor is ordinary salt (NaCl), which in multiple sclerosis has been shown to influence the disease course negatively through induction of Th17 cells.[57] Recent reports have also found Th17 to be an important factor in chronic gastrointestinal inflammation.[58]

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Yet, other environmental factors could of course be responsible for the onset of MC. Infectious agents could be one such possibility. Infection with *Helicobacter pylori* is inversely associated to MC.[59] The decrease in the prevalence of *Helicobacter Pylori* in the Western world is paralleled with an increase in MC;[1,9] the rationale for this hypothesis is well worth exploring further. Furthermore, a seasonal pattern with more cases of LC during the summer has been observed, something that could have many explanations.[60] The authors speculate that infections could have a role in the seasonal variation.

Consequently, despite a large cohort with a long follow-up, no association could be found between intake of protein, carbohydrates, different types of fat, fibre or zinc and occurrence of MC. BMI, education or physical activity did not confer any increased risk either. The previously observed risk increase in smoking and the female gender could be verified. Furthermore, high intake of alcohol seems to increase the risk for MC, although the smoking-related risk was modified by alcohol *per se*. The mechanisms behind these effects of alcohol have to be studied further in an investigation aimed at exploring this phenomenon.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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