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Diarrhoea is not the only symptom that needs to be treated in patients with microscopic colitis

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Abstract

Background: Many patients with microscopic colitis (MC) also suffer from symptoms of irritable bowel syndrome (IBS), but the only treatment given is corticosteroids for the diarrhoea. The aim of this study was to examine how social factors, life style factors and drug treatment affect symptoms and well-being in patients suffering from MC.

Methods: Women, over the age of 73 years, with biopsy-verified MC, at any Departments of Gastroenterology, Skåne, between 2002 and 2010 were invited. The questionnaires Gastrointestinal Symptom Rating Scale (GSRS) and Psychological General Well-being Index (PGWB) were sent by mail, along with questions about social and life style factors, and medical history.

Results: Of 240 invited, 158 patients (66%) were included (median age 63 years, range 27–73 years). Only 26% had never smoked. Smoking and concomitant IBS was associated with both impaired gastrointestinal symptoms (OR = 3.96, 95% CI = 1.47–10.66 and OR = 4.40, 95% CI = 2.09–9.26, respectively) and impaired psychological well-being (OR = 2.77, 95% CI = 1.04–7.34) and OR = 3.82, 95% CI = 1.83–7.99, respectively). Treatment with proton pump inhibitors (PPI) was associated with increased gastrointestinal symptoms (OR = 3.44, 95% CI = 1.45–8.16). Age, social factors, and corticosteroids had no effect on symptoms or well-being. Smoking was the only risk factor associated with IBS (OR = 2.68, 95% CI = 1.115–6.26).

Conclusion: Smoking and IBS are associated with impaired gastrointestinal symptoms and psychological well-being in MC patients. PPI is associated with impaired gastrointestinal symptoms.

Introduction

Microscopic colitis (MC) is a an overall term for two conditions, collagenous colitis (CC) and lymphocytic colitis (LC), both characterized by chronic or recurrent watery diarrhoea, normal or near-normal endoscopic appearance, and specific microscopic abnormalities in colonic biopsies. However, these two disease entities can be considered together and stratified for subtypes [1]. Some studies have shown a female predominance in both CC and LC [2], mainly affecting middle-aged women, whereas others have not been able to confirm this in LC [3, 4]. The aetiology to MC is unknown, but autoimmunity, inflammation and bile acid malabsorption have been suggested [2, 5]. It is described that MC impairs health-related quality of life (HRQOL) [6]. Several studies have shown a symptomatic overlap between MC and irritable bowel syndrome (IBS) [7, 8], and the combination of these two diseases further impairs gastrointestinal symptoms and psychological well-being [8]. The great overlap between IBS and MC, the fact that 63% of MC patients only have a single attack of diarrhoea, and the wide range of conditions rendering secondary MC, may lead to an inaccurate diagnose-setting [1, 3, 9]. Regarding inflammatory bowel disease (IBD), a consensus has been stated that requires at least one relapse of the disease before a final diagnosis [10]. This requirement is not at hand for MC, but has to be considered for the future. Irritable bowel syndrome is more common in women than in men, and as HRQOL and experiences of symptoms differ between genders, both IBS and MC should be studied separately for women and men [11].

Life style factors such us smoking, drinking and physical activity may be of importance, since these factors affect the gastrointestinal tract, psychological well-being, and HRQOL [12, 13, 14]. Smoking is a known risk factor for developing MC [15], but its effect on symptoms when the disease is present has never been examined. The wine consumption amongst women has been steadily increasing in Sweden during the last decades, coincident

with the same time interval when MC has increased in incidence [2, 16]. It is known that women are more vulnerable to alcohol than men [17]. The effect of physical activity on symptoms in MC has never been studied, although physical activity has a positive effect on IBS symptoms [13]. The patients are elder, thus often retired and living alone, which could further impair psychological well-being.

Corticosteroid treatment is considered the gold standard as treatment of MC, and is the drug most frequently prescribed [2, 5]. As more than half of the patients suffer from abdominal pain in addition to MC, treatment with sole corticosteroids should not be enough [8]. The goal for the treatment must be to improve all gastrointestinal symptoms and psychological well-being, why it is important to identify factors influencing these aspects. The aim of the present study was to examine the influence of social and life style factors such as marital status, education degree, employment, smoking habits, wine consumption, physical activity and drug treatment on gastrointestinal symptoms and psychological well-being in patients suffering from MC.

Methods

The study protocol was approved by the Ethics Committee of Lund University, and all participants gave written, informed consent when taking part in the study. The participation in the study was voluntary, with the possibility of withdrawal at any stage without any consequences, and that their responses would be treated confidentially.

Patients

Women who had been treated for MC at any outpatient clinic of the Departments of Gastroenterology, Skåne, between 2002 and 2010, were identified by search for the ICD-10 classification for the two forms collagenous colitis (CC) and lymphocytic colitis (LC). Only the 240 patients who had the diagnoses verified by colonic biopsy and were at the age of 73 years or younger, were invited to participate in the present study. About one-third of the total numbers of identified patients were excluded due to age above 73 years, as they had many other concomitant diseases and drug therapies. Altogether, 159 of the 240 invited patients accepted and were recruited to the study, but one patient was excluded due to another IBD diagnosis a few weeks after the inclusion. Leaving 158 patients (66%), and out of these, 133 (55%) also agreed to provide blood samples. These patients represent the majority of female cases of diagnosed MC in the most southern parts of Sweden under the age of 73 years.

Study Design

Between March and June 2011, invitations including study information and questionnaires about marital status, education, employment, smoking habits, wine consumption, physical activity, medical history, gastrointestinal symptoms, psychological well-being and Rome III criteria were sent by mail to all 240 women. They were also invited to visit the outpatient clinics of the Departments of Gastroenterology, Skåne University

Hospital, Malmö or Central Hospital in Kristianstad, to provide blood samples for routine analyses at the Departments of Laboratory Medicine in Skåne at respective hospital. Questionnaires were completed 1–3 weeks before blood samples were collected. A reminding letter was sent a month after the invitation letter to those who hadn't answered. Medical records were scrutinized and age, gastrointestinal symptoms, duration of symptoms, examinations, and treatments were recorded. Patients were divided into two groups. One group included patients with at least two episodes of watery diarrhoea; and/or dependent on long-term treatment of corticosteroids to maintain remission; and/or two pathological intestinal mucosa biopsies (MC1, n = 88). The other group included patients who had concomitant coeliac disease (11 cases), had gone through an acute gastroenteritis briefly prior to the diagnostic colonoscopy (4 cases), only had had one episode of severe diarrhoea, or had had a normal biopsy after the initial pathological intestinal biopsy, along with clinical remission (MC2, n = 70).

Questionnaires

Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a Swedish, disease-specific and self-administered questionnaire, designed to evaluate perceived severity of gastrointestinal symptoms during the previous week [18, 19, 20]. The questionnaire includes 15 items and uses a 7-grade Likert scale. This gives a total range value between 15 and 105 where the highest score (seven) represent the most pronounced symptoms and the lowest (one) no symptoms. The items are divided into five dimensions representing Reflux Syndrome (two items), Abdominal Pain Syndrome (three items), Constipation Syndrome (three items), Indigestion Syndrome (four items) and Diarrhoea Syndrome (three items). Norm values for healthy, gender-matched population is available. The control group consists of 2,162 subjects (median age 51 (range 19-84) years), out of 4,624 individuals from the city of Malmö, Sweden. Selection of the individuals was

performed using a computerized allocation program. The strata consisted of women and men in six age groups [21].

Psychological General Well-Being Index (PGWB)

The PGWB is a broad questionnaire to measure subjective well-being or distress during the previous week [22]. The questionnaire includes 22 items and uses a 6-grade Likert scale. This gives a total range value between 22 and 132 where a low score (one) correspond to a poor level of well-being and the higher value, the better psychological well-being. The items are divided into six dimensions representing Anxiety (five items), Depressed mood (three items), Positive well-being (four items), Self-control (three items), General health (three items) and Vitality (four items). Norm values for healthy, gender-matched population is available, see above [21].

Rome III criteria

The patients completed a shortened version of the Rome III questionnaire, only including IBS symptoms [23]. This questionnaire has been translated and validated into the Swedish language (Magnus Simrén and Anna Rydén). Patients who fulfilled the criteria for Rome III were classified as also suffering from IBS, but as their diagnosis was MC, we have in accordance to its presence in IBD, called it IBS-like symptoms [8].

Statistical analyses

Statistical calculations were performed in SPSS, version 20.0 for Windows[©]. First, the distribution was tested using a one-sample Kolmogorov-Smirnov test. All distributions differed significantly (p<0.05) from a normal distribution, why studied factors were categorized. Values are given as median (interquartile range). We used simple mean imputation for missing data in GSRS and PGWB, when at least 50% of the items had been completed. There was no difference between CC and LC in the GSRS or PGWB scores or

patient characteristics (data not shown), why all calculations were performed on the whole

MC group, independent of CC or LC. The scores of the GSRS and PGWB were divided into

dichotomy variables to get low or high values in the questionnaires. The dichotomy of best

physical and psychological well-being was set as reference. Age was divided into 5-years

intervals. The cohort was divided into quartiles of the number of days drinking wine, and the

average number of minutes exercising per week during the year. Smoking was divided into

three categories: subjects who had never smoked, subjects who had stopped smoking, and

current smokers, including both regular and occasional smokers. Employment was divided

into three categories: employed, retired, or others, where others included housewives, students

or unemployed. There were missing values in wine consumption and education degree, which

were labelled as an own category. The first category was used as reference. Factors intended

to study (independent variables), namely, age, marital status, education degree, employment,

smoking habits, days of wine consumption per month, physical activity in minutes per week,

drug treatment for gastrointestinal symptoms, and presence of IBS, were initially examined

using univariate analyses. Factors with p<0.05 were included in multiple logistic regression

analysis to calculate odds ratios with 95% confidence intervals (OR with 95% CI) in MC

patients with high compared to low values of gastrointestinal symptoms and psychological

well-being (dependent variables). Subgroup analyses were performed in the same way in the

patient groups MC1 and IBS. To calculate on the risk factors for developing IBS within this

cohort, the variable labelling IBS as "yes" o "no" was used as dependent variable in a separate

analysis. Mann-Whitney U-test and Fisher´s exact test were used for calculation between

groups. *P*<0.05 was considered to be statistically significant.

Results

Patient characteristics

In total, 158 women with MC were included in the study (median age 63 years, range 27–73 years), CC was diagnosed in 92 patients (58%) (median age 64 years, range 31–73 years) and LC in 66 patients (42%) (median age 63 years, range 27–72 years). Of these 158, 87 patients (55%) also fulfilled the Rome III criteria for IBS (median age 63 years, range 27–72 years), 49 of the patients (53%) with CC and 38 of the patients (58%) with LC (Table 1). There was no difference in age between patients with or without IBS-like symptoms (median age 63 years, range 27–73 years, and median age 64 years, range 28–73 years, respectively, p = 0.134). Neither was there any difference in disease duration between the two groups (median 9 years, range 1–45 years, and median 6 years, range 1–50 years, respectively, p = 0.103). Measurements of haemoglobin (Hb) in blood and C-reactive protein (CRP) in plasma were in the majority of patients within reference values, and did not reveal any differences in patients who fulfilled the Rome III criteria or not (p = 0.367 and p = 0.307, respectively).

No one of the patients was in an acute, severe relapse, but were in remission during inclusion; either a spontaneous remission or under treatment with corticosteroids (30.4%). Many of the patients were also treated with proton pump inhibitors (PPI), but there was no association between the use of these two drugs (p = 0.329) (Table 1). Only 20.1% of the patients had MC as the sole diagnosis, hypertension (34.2%), allergy (31.0%), rheumatoid arthritis (20.9%), goitre or thyroid dysfunction (22.2%), and asthma (15.8%) being the most prevalent concomitant diseases. Besides treatment with PPI and corticosteroids, the patients often were treated with thyroid hormones (19.0%) antidepressant drugs of the type selective

serotonin reuptake inhibitors (19.0%), statins (17.7%), and angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (17.1%).

Fifty-six percent of patients were married. Twelve percent told they were single; 22.2 % were divorced and 8.9 % widow, respectively. Higher education was classified as education after college, and 39.2 % of patients had some sort of such education. About half of the patients were retired (Table 1).

Smoking habits

Among smokers, two-thirds smoked regularly, whereas one-third smoked occasionally. A great deal of the patients had stopped smoking (Table 2). Nine percent of the patients used nicotine chewing and 2.5% of the patients were taking nicotine stuff. Patients with higher education smoked to a lesser extent than those who had no university degree (p=0.035).

Wine consumption

After debut of the disease, 22.2% had changed drinking habits, whilst 76.6 % had not done it. In the fourth quartile of wine consumption, 33% of the women had a wine consumption over the Swedish recommendations of <9 glasses/week (1 glass defined as 12g 100% pure alcohol = 15 cl wine) [24]. The consumption of beer and liquid was almost absent in this patient group, except in women drinking wine most days in month, who also drank liquid now and then (data not shown). The vast majority of women consumed 1–2 glasses of wine each day they were drinking. The women with education after college had the lowest wine consumption counted as days/month (p < 0.001). Patients who were treated with corticosteroids or PPI had a tendency to lower wine consumption than patients not using these drugs (p = 0.073 and p = 0.062, respectively).

Physical activity

The patients had to declare how many minutes/week they had physical activity, including travelling to and from their works. The degree of total physical activity was highest in the summer (300 (180–442) min/week) and lowest in the winter (200 (120–300) min/week).

Gastrointestinal symptoms and psychological well-being

Both gastrointestinal symptoms and psychological well-being were deteriorated in patients compared to healthy female controls. All dimensions except depressed mood were impaired in patients (Table 3). Age and physical activity did not influence either gastrointestinal symptoms or psychological well-being (data not shown). Smoking was associated with impaired gastrointestinal symptoms and gastrointestinal well-being. The amount of wine drinking in this study did not affect gastrointestinal symptoms or psychological well-being. The presence of concomitant IBS-like symptoms had a negative impact on both gastrointestinal symptoms and psychological well-being. Treatment by PPI or corticosteroids did not affect PGWB, but those who did use PPI had increased gastrointestinal symptoms (Table 4). Patients treated with PPI had more pronounced symptoms in all dimensions in GSRS compared to non-treated (reflux, p = 0.000; abdominl pain, p = 0.002; constipation, p = 0.005; indigestion, p = 0.033; diarrhoea, p = 0.046; total scores, p = 0.001). Marital status, education degree or employment did not affect the total scores of GSRS or PGWB (Table 4).

Patients with primary, relapsing microscopic colitis at follow-up

There was no difference in total scores of PGWB or GSRS between the whole group of MC or those with primary, persistent MC (MC1) (Table 3). In the MC1 group, the concomitant presence of IBS or PPI use increased abdominal complaints (OR =3.37, 95% CI = 1.23–9.19 and OR = 3.54, 95% CI 1.10–11.39, respectively), whereas moderate physical activity improved symptoms (second quartile, 139-245 min/week; OR = 0.15, 95% CI =0.03–

0.83). The only factor that impaired psychological well-being in patients with consistent MC was IBS (OR = 4.60, 95% CI = 1.17–12.36).

Patients with irritable bowel syndrome

Patients with IBS only had impaired scores for the dimensions abdominal pain and constipation compared to the whole MC group (Table 3). The only life style factor measured that affected whether the patient fulfilled IBS criteria or not was smoking, which increased the risk for also suffering from IBS-like symptoms (OR = 2.68, 95% CI = 1.115–6.26). If only calculation of gastrointestinal symptoms and psychological well-being on patients with IBS were performed, none of the life style factors influenced the gastrointestinal symptoms, whereas alcohol drinking 6–10 days a month and >10 days a month (OR = 0.24, 95% CI = 0.07–0.83 and OR = 0.17, 95% CI = 0.04–0.76, respectively) and moderate physical activity (third quartile, 240–420 min/week; OR = 0.13, 95% CI = 0.02–0.83) improved the psychological well-being.

Discussion

Smoking and IBS-like symptoms were the factors most affecting gastrointestinal symptoms and psychological well-being in patients suffering from MC. Treatment with corticosteroids did not affect the total scores of symptoms or well-being. Wine drinking did not affect gastrointestinal symptoms or psychological well-being in the whole group of MC patients. Treatment by PPI was associated with increased gastrointestinal symptoms. Also after analyses in patients with only primary, persistent MC were performed, the same results were found. Smoking was an increased risk for suffering from IBS-like symptoms. Age and social factors did not affect the clinical picture in MC patients.

Microscopic colitis is considered to be a disease characterized by watery diarrhoea of autoimmune aetiology, and treatment of the diarrhoea by corticosteroids is the gold standard in the handling of these patients when the symptoms are relapsing [2, 5]. However, corticosteroids only reduce the diarrhoea caused by MC and have no place in the treatment of IBS [23, 25]. Patients treated with corticosteroids in the present study did not have reduced gastrointestinal symptoms compared to untreated patients. This is in accordance with the finding that MC patients suffer from many different gastrointestinal symptoms, not only diarrhoea, and suggests that only treatment of the diarrhoea is not enough. To improve the overall gastrointestinal symptoms and psychological well-being must also be taken into consideration. Treatment with PPI did not improve gastrointestinal symptoms, which further underlines the conclusion that PPI has no place in the treatment of IBS [25, 26]. Irritable bowel syndrome and other functional bowel syndromes are mainly affecting younger persons [23, 25], whereas our patients with MC are older. The gastrointestinal symptoms in our cohort may in some patients with concomitant drug treatments represent side effects by the drugs, rather than true IBS, and as the patients also suffered from MC, we have chosen to use the term IBS-like symptoms.

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Smoking has been described as a risk factor for developing MC [5, 15]. Smoking has also been described as a risk factor for developing post-infectious functional gastrointestinal disorders (FGID) [27], and for overlapping syndromes between reflux diseases and FGID [28]. Although an intense research to find out the aetiology to IBS and other functional bowel diseases have been conducted the last decades, very few studies have investigated the effect of smoking on functional disorders. One previous study has described that smoking rendered symptoms of functional dyspepsia, but not IBS [12]. Another study has shown that both visceral and peripheral pain is increased by smoking [29]. The result of the present study with impaired gastrointestinal symptoms in smoking, and increased risk for smokers to also have concomitant IBS-like symptoms, suggests that smoking cessation must be the first line of treatment in patients with MC and gastrointestinal symptoms. Impaired psychological well-being by smoking does not say anything about causality. The patients may suffer from anxiety, and because of this, they are unable to stop smoking. Smoking has to be considered as a confounding factor when measuring health-related quality of life. Even after subgroup analyses, smoking and IBS turned out to be the most important risk factors for impaired symptoms and well-being in patients with MC. The MC group with persistent, primary symptoms (MC1) differed in symptoms from the total MC group in these aspects, as smoking did not worsen the symptoms.

Chronic alcohol exposure is known to have a number of deleterious effects on the intestinal mucosa. In animal experiments, alcohol leads to increased oxidative stress, hyperpermeability, neuropathy and dysbiosis which favour and sustain local inflammation [30, 31]. In cell culture of monolayers of intestinal cells, ethanol induces disruption of the F-actin cytoskeleton and of intestinal barrier integrity. The mechanism underlying this pathophysiological effect on barrier integrity appears to involve instability of the assembly of the subunit components of actin network [32, 33]. Findings support the hypothesis that the

cytoskeleton may be a major target for injury in damaged intestinal epithelium [34]. In accordance, ethanol can be used in mice to develop an inflammatory reaction in the colon characterized by an intense inflammatory infiltrate in the mucosa and submucosa [35].

The effect of alcohol drinking on gastrointestinal symptoms in human is inconsistent. Some studies have shown that alcohol impairs symptoms [14], whereas others have shown that alcohol has no effect on functional gastrointestinal symptoms [12]. Alcohol may trigger relapses and pronounced symptoms in patients with already developed IBD [36], which could not be seen in our study for the MC patients. The effect measured on symptoms reasonably has to be connected to the volume consumed. The women in the present study mainly drank wine, and the consumption of beer and liquid was inconsiderable. The majority of patients were drinking 1-2 glasses a day when drinking. Furthermore, red wine, which contains phenolic compounds, has been shown to affect the composition of human gut microbiota [37]. Phenolic compounds of red wine down-regulated serum concentrations of several cytokines and inflammatory markers, whereas others were increased [38]. Thus, the effect of ethanol in red wine may be counterbalanced by phenolic compounds. Recently, it has been shown that the alcohol consumption is higher among more well-educated persons [39]. However, this was not the truth in the present study including most elder women. We could not find any effect of marital status, education degree, or employment degree on psychological well-being.

In this study, we could not find any correlation between gastrointestinal symptoms or psychological well-being and physical activity in the whole MC group. When performing subgroup analyses, gastrointestinal symptoms were improved by moderate physical activity in the MC1 group, in accordance with previous studies describing improvement of IBS symptoms after training [13]. However, these results may be interpreted

with caution, as they may reflect that women with more severe disease are not able to exercise, but have to stay at home, close to the toilet.

Learning points

Taken together, smoking and concurrent presence of IBS-like symptoms in addition to diarrhoea are the factors most important to determine gastrointestinal symptoms and psychological well-being in MC patients. To be aware of this, to encourage smoking cessation, and to treat all the patient´s gastrointestinal symptoms must be emphasized among health care professionals. Treatment by PPI is associated with increased gastrointestinal symptoms in patients suffering from MC.

Conflicts of interest: There is no conflict of interests.

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Table 1. Patient characteristics in the patients included with microscopic colitis

	All patients included n = 158	MC1 n = 88	IBS n = 87
Age (year)	63 (58–67)	63 (56–68)	62 (56–67)
Duration (year**)**	6 (4–14)	10 (4–16)	9 (4–16)
Body mass index (kg/m^2)	24.88 (22.61–28.72)	24.09 (21.69–27.51)	24.60 (22.85–29.15)
missing	42 (26.6)	38 (43.2)	39 (44.8)
Higher education* (n, %)	62 (39.2)	38 (43.2)	35 (40.2)
Employed/Retired (n, %)	70 (44.3) /79 (50.0)	43 (48.9)	42 (48.3)/40 (46.0)
Married (n, %)	89 (56.3)	49 (55.7)	48 (55.2)
Smoking habits (n, %)			
Never smoked	41 (25.9)	27 (30.7)	19 (21.8)
Have stopped smoking	64 (40.5)	26 (29.5)	31 (35.6)
Current smokers	53 (33.5)	35 (39.8)	37 (42.5)
Days/month of wine drinking (n, %) missing	9 (5.7)	4 (4.5)	3 (3.4)
0-2	69 (43.7)	42 (47.7)	38 (43.7)
3-5	24 (15.2)	10 (11.4)	14 (16.1)
6-10	34 (21.5)	22 (25.0)	20 (23.0)
>10	22 (13.9)	9 (10.2)	12 (13.8)
Drug treatment (n, %)			
Proton pump inhibitors	41 (25.9)	27 (30.7)	25 (28.7)
Steroids	48 (30.4)	34 (38.6)	31 (35.6)
Irritable bowel syndrome (n, %)	87 (55.1)	48 (54.5)	

Patients are shown as all patients included, and divided into patients with consistent findings of primary MC

(MC1) or irritable bowel syndrome (IBS). *Higher education was classified as education after college

Table 2. Association between wine consumption and smoking

	0-2 days (%)	3-5 days (%)	6-10 days (%)	>10 days (%)
Never smoked (missing 4.9)	51.2	14.6	22.0	7.3
Stopped smoking (missing 4.7)	31.3	21.9	23.4	18.2
Current smokers (missing 7.5)	52.8	7.5	18.9	13.2

Fisher´s exact test, p=0.194. Wine consumption is divided into quartiles based on the number of days drinking wine monthly.

Table 3. Values of Gastrointestinal Symptom Rating Scale (GSRS) and Psychological

General Well-Being (PGWB) in patients with microscopic colitis and healthy females

	All patients n = 158 Mean, 95% CI	MC1 n = 88 Mean, 95% CI	IBS n = 87 Mean, 95% CI	Healthy females n = 2,162 Mean ,95% CI
Abdominal pain	4.00 3.74–4.26	3.97 3.59–4.35	4.70 4.39–5.02	1.63 1.58–1.68
Indigestion	2.98 2.81–3.15	2.92 2.68–3.15	3.35 3.12–3.58	1.78 1.73–1.83
Reflux	2.40 2.22–2.59	2.45 2.19–2.72	2.74 2.49–2.99	1.37 1.33–1.42
Constipation	3.38 3.15–3.62	3.56 3.23–3.90	3.96 3.66–4.26	1.65 1.59–1.71
Diarrhoea	3.68 3.43–3.93	3.95 3.61–4.29	4.16 3.84–4.47	1.39 1.35–1.43
GSRS Total	3.06 2.90–33.22	3.14 2.92–3.36	3.51 3.33–3.69	1.56 1.52–1.59
Anxiety	22.51 21.72–23.30	22.54 21.48–23.60	21.30 20.23–22.36	23.62 23.31–23.92
Depressed mood	14.74 14.29–15.18	14.87 14.29–15.44	13.93 13.34–14.51	15.31 15.13–15.49
Positive well-being	14.58 13.96–15.20	14.35 13.54–15.16	13.78 12.94–14.61	15.95 15.70–16.21
Self-control	14.36 13.91–14.82	14.28 13.69–14.87	13.74 13.08–14.40	15.06 14.88–15.23
General health	12.84 12.33–13.35	12.93 12.29–13.56	11.88 11.22–12.53	14.41 14.21–14.26
Vitality	14.70 14.01–15.40	14.67 13.77–15.58	13.88 12.94–14.81	16.95 16.69–17.21
General well-being Total	93.76 90.69–96.78	93.64 89.75–97.53	88.49 84.45–92.54	101.41 100.23–102.60

The patients with microscopic colitis (MC) were divided into all patients and patients with

consistent findings of primary MC (MC1). Data of healthy females referred from reference

No 21.

Table 4. Univariate and multivariate analyses of risk factors for impaired gastrointestinal symptoms and psychological well-being

	GSRS		PGWB	
	Crude OR 95% CI	OR 95% CI	Crude OR 95% CI	OR 95% CI
Smoking habits				
Never smoked (reference)	1.00	1.00	1.00	1.00
Stopped smoking	0.96 (0.43–2.16)	1.11 (0.44–2.75)	1.53 (0.68–3.41)	2.19 (0.86–5.58)
Current smokers	3.80 (1.59–9.07)	3.96 (1.47–10.66)	3.10 (1.33–7.24)	2.77 (1.04–7.34)
Days of drinking/month				
0-2 (reference)	1.00		1.00	1.00
3-5	0.82 (0.32-2.07)		0.72 (0.28–1.84)	0.70 (0.24–2.05)
6-10	1.03 (0.45-2.36)		0.72 (0.32–1.65)	0.72 (0.27–1.92)
>10	0.47 (0.17-1.25)		0.34 (0.12–0.94)	0.32 (0.10–1.05)
missing data (9 (5.7%))	0.23 (0.04-1.20)		0.36 (0.08–1.57)	0.39 (0.08–2.00)
Marital status				
Married (reference)	1.00		1.00	
Living alone	1.11 (0.59–2.09)		1.55 (0.82–2.93)	
Education degree				
Low education (reference)	1.00		1.00	
High education	1..548 (0.77–2.82)		1.00 (0.52–1.90)	
Missing (4 (2.5%))	0.38 (0.04–3.79)		1.00 (0.14–7.40)	
Employment				
Employed (reference)	1.00		1.00	
Retired	1.21 (0.64–2.30)		0.63 (0.33–1.21)	
Others (9 (5.7%))*	1.40 (0.35–5.60)		0.99 (0.25–4.02)	
Irritable bowel syndrome				
No IBS (reference)	1.00	1.00	1.00	1.00
Presence of IBS	4.67 (2.37–9.20)	4.40 (2.09–9..26)	4.23 (2.17–8.27)	3.82 (1.83–7.99)
Drug treatment				
No use of PPI (reference)	1.00	1.00	1.00	1.00
Use of PPI	2.74 (1.29–5.83)	3.44 (1.45–8.16)	2.09 (1.01–4.35)	2.00 (0.85–4.68)
No use of steroids (reference)	1.00		1.00	1.00
Use of steroids	1.25 (0.63–2.47)		2.36 (1.17–4.75)	1.86 (0.82–4.18)

The number of days of wine drinking was divided into quartiles of the consumption. OR=Odds ratio, CI=confidence interval, GSRS=Gastrointestinal Symptom Rating Scale, PGWB=Psychological General Well-Being, IBS=Irritable bowel syndrome, PPI=Proton pump inhibitors. GSRS and PGWB were divided into two groups, where the best well-being was set as reference. *= Includes housewife, students and unemployed.