


Demographic and clinical features distinguish subgroups of diverticular disease patients: Results from an Italian nationwide registry

Marilia Carabotti¹, Rosario Cuomo², Giovanni Barbara³, Fabio Pace⁴,
Paolo Andreozzi², Cesare Cremon³  and Bruno Annibale¹;
on behalf of the REMAD Group

Abstract

Background: Clinical features and lifestyle factors associated with diverticulosis compared to diverticular disease (DD), either symptomatic uncomplicated diverticular disease (SUDD) or in patients who have had previous diverticulitis (PD), are unclear.

Objective: The objective of this article is to compare cross-sectionally demographic and clinical features and quality of life (QoL) in diverticulosis, SUDD and PD patients.

Methods: The REMAD Registry is a prospective, observational, multicentre, cohort study. Patients were categorised according to: diverticulosis; SUDD (recurrent abdominal symptoms attributed to diverticula in absence of overt inflammation) and PD (≥ 1 previous diverticulitis).

Results: A total of 1217 patients (57.9% diverticulosis, 24.7% SUDD and 17.4% PD) were included. Compared to diverticulosis, female gender was associated to SUDD (OR 1.94; 95% CI: 1.43–2.62) and PD (OR 1.79; 95% CI: 1.24–2.56); age ≤ 60 years was associated to PD (OR 2.10; 95% CI: 1.42–3.08 vs diverticulosis, OR 1.57; 95% CI: 1.01–2.45 vs SUDD). PD patients showed an association with past bleeding (OR 29.29; 95% CI: 8.17–104.98 vs diverticulosis, OR 16.84; 95% CI: 3.77–75.25 vs SUDD). Compared to diverticulosis, family history for diverticula was associated to PD (OR 1.88; 95% CI: 1.27–2.78). Patients with diverticulosis showed higher QoL scores, both physical ($p = 0.0001$ and 0.0257) and mental ($p < 0.0001$ and 0.0038), in comparison to SUDD and PD.

Conclusion: Family history for diverticula and history of bleeding distinguish diverticulosis from DD. These clinical features should be kept in mind in the management of DD.

Keywords

Diverticulosis, symptomatic uncomplicated diverticular disease, previous diverticulitis, clinical characteristics, registry

Received: 16 November 2017; accepted: 22 February 2018

Key summary

- Despite the high prevalence of colonic diverticulosis and diverticular disease, most data on clinical characteristics are based on hospitalised patients and do not consider asymptomatic or uncomplicated individuals, who represent the majority of patients.
- This nationwide registry study showed that specific demographic and clinical features distinguish subgroups of diverticular disease patients, in particular past diverticular bleeding and family history of colonic diverticula are more prevalent in patients who have had a previous episode of diverticulitis.

¹Medical-Surgical Department of Clinical Sciences and Translational Medicine, University Sapienza, Roma, Italy

²Department of Clinical Medicine and Surgery, Federico II University, Napoli, Italy

³Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

⁴Unit of Gastroenterology, “Bolognini” Hospital, Bergamo, Italy

Corresponding author:

Bruno Annibale, Medical-Surgical Department of Clinical Sciences and Translational Medicine, University Sapienza, Via di Grottarossa 1035-1039, 00189 Rome, Italy.
Email: bruno.annibale@uniroma1.it

- These clinical anamnestic remarks, associated to the perceived worse quality of life in symptomatic uncomplicated diverticular disease and in patients who have had a previous episode of diverticulitis, should be kept in mind in the management of this condition, including its therapeutic regimens.

Introduction

Colonic diverticula are common in Western countries and their prevalence increases with age, affecting up to 60% of individuals over 70 years of age.¹ The majority of patients with colonic diverticula remain asymptomatic (diverticulosis), while about 20% develop recurrent abdominal symptoms, including abdominal pain, bloating and changes in bowel habits, a condition termed symptomatic uncomplicated diverticular disease (SUDD). Abdominal complaints observed in SUDD may be similar to those of irritable bowel syndrome (IBS) but some abdominal pain features, for example, pain localisation, pain relief by defecation or flatulence, and pain duration, have been described to differentiate these two disorders.²⁻⁴ About 4% of patients develop complications including acute diverticulitis, even as those confirmed by computed tomography (CT) or surgically are 1%.⁵ This rather small percentage contradicts the common belief that diverticulosis has a high rate of progression.^{5,6}

Despite the high prevalence of this condition and its relative economic burden, most data from epidemiological studies have used hospitalised patients, thereby omitting asymptomatic diverticulosis or uncomplicated individuals, who represent the majority of patients.^{7,8} In fact, available data have focused their attention mainly on risk factors associated to the development of diverticulosis or its complications, advocating the importance of many lifestyles factors, such as smoking, physical activity or dietary habits, providing discordant results.⁹ The role of dietary fibre in diverticular disease (DD) is controversial since on one hand, a high-fibre diet is associated with an higher prevalence of colonic diverticula,¹⁰ whereas its intake reduces the risk of hospitalisation for diverticulitis.¹¹

Studies specifically aimed at addressing clinical features and lifestyle factors associated with asymptomatic diverticulosis, in comparison to DD, either in its uncomplicated presentation, such as SUDD, or in patients who have had a previous diverticulitis (PD), are substantially lacking.

The aim of this study was to assess specific clinical features, lifestyle factors and quality of life (QoL) in patients with colonic diverticulosis, SUDD and PD in order to identify specific characteristics associated to each subgroup of patients.

Materials and methods

Study design and population

The Italian Study Group on Diverticular Disease (GrIMAD) scientific association promoted the Diverticular Disease Registry (REMAD), an ongoing five-year prospective, observational, multicentre, cohort study. The main purpose of this registry was to understand the natural history of diverticulosis and DD, with follow-up assessment scheduled every six months. This cross-sectional study analysed the baseline characteristics of the cohort to assess possible differences between subgroups of patients.

Forty-seven centres, academic and non-academic, were selected in the North (50.1%), Centre (18.3%) and South (31.6%) of Italy. Each centre was required to recruit at least consecutive 20 patients during two months. During the two-month recruitment period, patients were consecutively enrolled. Inclusion criteria were: informed consent; age ≥ 18 years; endoscopic/radiological-confirmed colonic diverticula. Exclusion criteria were: failure to sign informed consent; inability to adhere to the study procedures. Each patient who met the inclusion criteria was invited to take part in the study, regardless of the presence of symptoms or the reason for consultation in the centre. The mean rate of non-adhering patients in the registry in all participant centres was $24\% \pm 8.3$. A total of 1255 consecutive patients were initially considered, but five centres which included fewer than 20 patients (total of 38 patients) were a priori excluded.

After the ethical approval of the coordinator centre (University Federico II, Naples n. 161/14, 24 September 2014), local ethical approvals were obtained from the other centres.

The REMAD Registry is registered as an observational study in ClinicalTrial.gov (ID: NCT03325829). All patients gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Data collection

The present study considered the following data: personal characteristics (gender, age, ethnicity, body mass index (BMI)); centre of enrolment, reasons and modalities for diagnosis of colonic diverticula; clinical characteristics (history of diverticular bleeding; first-degree family history for colonic cancer and for diverticula;

comorbidities expressed as Charlson index;¹² lifestyle factors (smoking (active, former and ever smokers); regular alcohol and coffee drinking; physical activity (active or inactive patient)); dietary amount of food rich in fibre (weekly number of consumption of vegetables, fruits, whole cereals). QoL was assessed by means of SF-12 questionnaires, with evaluation of physical and mental component summary scores.¹³

At entry, patients were categorised into three subgroups according to the following criteria:

- (a) diverticulosis defined as presence of colonic diverticula in the absence of abdominal symptoms;¹⁴
- (b) SUDD defined as recurrent abdominal pain, mainly in the lower abdominal quadrants, with a frequency of at least once weekly, present for at least six months, and/or changes in bowel habit, without a well-defined previous attack of acute diverticulitis;^{4,15}
- (c) PD patients who have experienced at least one episode of acute diverticulitis, complicated or not; when available medical charts were also reviewed. At time of inclusion patients reported having or not having gastrointestinal (GI) symptoms.

To categorise patients into the three groups, GI symptoms were quantified by use of three standardised symptoms questionnaires (questionnaire for abdominal pain lasting less than 24 hours; questionnaire for abdominal pain lasting more than 24 hours; questionnaire for IBS following Rome III), as previous published.^{3,4}

Statistical analysis

Data were expressed as percentage of total available data and mean \pm standard deviation. Univariate analyses were performed by *T* test, Fisher's exact and Chi squared test for categorical and continuous variables. Where appropriate, Kruskal–Wallis test was used to compare the three subgroups. Odds ratio (OR) and 95% confidence intervals (CIs), obtained by logistic regression analysis, were used to assess the presence of clinical features or lifestyle factors associated to each subgroup of patients. For comparison among groups, three logistic analyses were performed: (a) between diverticulosis vs SUDD; (b) between diverticulosis vs PD; and (c) between SUDD vs PD.

Logistic regression was adjusted for: female gender; age \leq 60 years; BMI \geq 30 kg/m²; past bleeding; family history of colonic cancer; family history of diverticula; Charlson index score \geq 3; active smoking; alcohol drinking; coffee drinking; physical activity; diet rich in fibre (consumption of fruits and/or vegetables and/or whole foods \geq 2/day). For the following variables data

were not complete, but missing data were lower than <1.5% (reason for diagnosis of colonic diverticula; family history of diverticula and colon cancer; smoking, alcohol, coffee consumption and physical activity), except for modalities for diagnosis of diverticula (5.6%), and dietary habits (7.7%). A two-tailed *p* value < 0.05 was considered statistically significant. Statistical analysis was carried out using a dedicated software package (MedCalc Software, Mariakerke, Belgium, version 12.2).

Results

Demographic characteristics

A total of 1217 patients were included in the REMAD Registry. Male gender was slightly prevalent (54.3%) and patients were almost all Caucasian (99.6%). The mean age was 66.1 \pm 9.9 years, and 24.5% of them were younger than 60 years old. The mean BMI was 26.1 \pm 3.9 kg/m². The majority of patients were enrolled in endoscopy units (50.5%) and in out-patient services (41.6%), whereas a smaller percentage was enrolled in GI or surgical wards (7.9%). Diagnosis of colonic diverticula was obtained by colonoscopy (77.1%), abdominal CT (10.6%), barium enema (5.1%), ultrasound (4%) and CT colonoscopy (3.2%).

At enrolment 57.9% (*n* = 705) of patients were classified as diverticulosis, 24.7% (*n* = 300) as SUDD and 17.4% (*n* = 212) as PD. In 47.9% of patients a diagnosis of colonic diverticula was confirmed in the absence of abdominal symptoms; in 20.4% the diagnosis was confirmed in the presence of symptoms but not pain, and in 31.7% in the presence of abdominal pain. The single reason allowing for the diagnosis of colonic diverticula for each subgroup of patients is reported in Table 1.

Data regarding gender for each subgroup of patients are shown in Table 2. There was a greater proportion of females in the SUDD (*p* < 0.0001) and PD groups (*p* = 0.003) compared to the diverticulosis group. Female gender was significantly associated to SUDD (OR 1.94; 95% CI: 1.43–2.62) and PD (OR 1.79; 95% CI: 1.24–2.56) in comparison to diverticulosis at logistic analysis (Table 3).

The mean age of the patients was 66.7 \pm 9.4, 66.2 \pm 9.5, and 63.9 \pm 11.5 years for diverticulosis, SUDD and PD, respectively. At univariate analysis, the PD subgroup was significantly younger in comparison both to diverticulosis (*p* = 0.0015) and SUDD (*p* = 0.0142). Considering the age distribution by decade, patients age \leq 49 and between 50 and 59 years were more prevalent in the PD subgroup, whereas in the decades 60–69 and 70–79 years, diverticulosis was significantly more prevalent compared to PD patients

Table 1. Reasons for diagnosis of colonic diverticula in diverticulosis, symptomatic uncomplicated diverticular disease and previous diverticulitis patients.

| | Diverticulosis <i>n</i> = 705 | SUDD <i>n</i> = 300 | PD <i>n</i> = 212 |
|---|----------------------------------|------------------------|----------------------|
| Absence of symptoms | | | |
| During colonoscopy for colon cancer screening (<i>n</i> = 510) | 91 | 6.9 | 2.1 |
| During radiology (<i>n</i> = 47) | 89.4 | 6.4 | 4.2 |
| Anaemia (<i>n</i> = 22) | 72.7 | 18.2 | 9.1 |
| Presence of symptoms but not pain | | | |
| Alteration of bowel habit (<i>n</i> = 106) | 64.1 | 25.5 | 10.4 |
| Bloating (<i>n</i> = 45) | 64.5 | 33.3 | 2.2 |
| Rectal bleeding (<i>n</i> = 89) | 59.6 | 15.7 | 24.7 |
| Fever (<i>n</i> = 7) | 14.3 | | 85.7 |
| Abdominal pain (<i>n</i> = 383) | 7.3 | 52.5 | 40.2 |

Data were expressed as percentage per row.

SUDD: symptomatic uncomplicated diverticular disease; PD: previous diverticulitis.

Table 2. Number of females and males in diverticulosis, symptomatic uncomplicated diverticular disease and previous diverticulitis patients.

| | Diverticulosis <i>n</i> = 705 | SUDD <i>n</i> = 300 | PD <i>n</i> = 212 |
|---------------------------------|----------------------------------|------------------------|----------------------|
| Female gender (<i>n</i> = 556) | 275 (39) | 174 (58) | 107 (50.5) |
| Male (<i>n</i> = 661) | 430 (61) | 126 (42) | 105 (49.5) |

N (% per column).

SUDD: symptomatic uncomplicated diverticular disease; PD: previous diverticulitis.

(Figure 1). At logistic regression, age ≤ 60 years was associated with PD in comparison both to diverticulosis (OR 2.10; 95% CI: 1.42–3.08) and SUDD (OR 1.57; 95% CI: 1.01–2.45) (Table 3). Even when we consider age in years as a continuous variable, logistic regression analysis showed that, compared to diverticulosis, PD diagnosis is associated to decrease in age (OR 0.97; 95% CI: 0.95–0.99).

Considering the overall population, females were older in comparison to male patients (67.1 ± 9.6 vs 65.2 ± 10.1 , $p = 0.0006$). Such an increase was specifically observed in SUDD and PD patients, being female and older in comparison to male (67.6 ± 8.8 vs 64.3 ± 10.3 , $p = 0.0029$; 65.9 ± 10.7 vs 61.7 ± 11.9 , $p = 0.007$). In fact, diverticulosis female and male age were not different (67.3 ± 9.7 vs 66.3 ± 9.3 , $p = 0.175$).

The mean BMI for each subgroup of patients was 26.2 ± 3.4 , 26.2 ± 3.9 and 25.6 ± 4.1 kg/m² for diverticulosis, SUDD and PD, respectively, without significant differences. Considering obese patients (BMI ≥ 30 kg/m²), no differences were observed (Table 3).

Clinical characteristics and lifestyle factors

History of bleeding attributed to colonic diverticula was reported in 0.6% and 1% of diverticulosis and SUDD patients, respectively. In PD, 4.2% of patients reported a history of diverticular bleeding separately from diverticulitis (Table 3).

Compared to diverticulosis and SUDD patients, PD showed a significant association with history of bleeding at univariate ($p = 0.0004$ and 0.0331 , respectively) and multivariate analysis (OR 29.29; 95% CI: 8.17–104.98 and OR 16.84; 95% CI: 3.77–75.25) (Table 3). A concomitant episode of diverticular bleeding as a complication of diverticulitis was present in 4.2% of PD patients.

No differences regarding the presence of family history of colonic cancer were observed at univariate or multivariate analysis. Family history of diverticula was significantly prevalent in PD patients in comparison to diverticulosis at univariate ($p = 0.0012$) and multivariate analysis (OR 1.88; 95% CI: 1.27–2.78) (Table 3). In addition, PD patients with a positive family history were significantly younger in comparison to those without (61.7 ± 7.9 and 64.8 ± 12.5 years, respectively, $p = 0.003$). No differences in the prevalence Charlson index score ≥ 3 were observed.

Concerning lifestyle factors, univariate analysis showed differences in smoking habit only regarding active smoking between PD and SUDD patients ($p = 0.0208$); however, this was not confirmed at logistic regression analysis (Table 3). Regarding alcohol intake, consumption of coffee and physical activity, no differences were observed both at univariate and multivariate analysis (Table 3). Regarding dietary habits, we analysed the amount consumed per week of foods rich in fibre such as fruits, vegetables and whole foods, without significant differences among subgroups at univariate analysis (Table S1). When we consider the consumption of a fibre-rich diet, no differences emerged at logistic regression analysis (Table 3).

QoL

Regarding physical component summary scores, patients with diverticulosis perceived a higher physical well-being score in comparison to SUDD (48.6 ± 8.5 vs 46.1 ± 9 , $p = 0.0001$) and PD (48.6 ± 8.5 vs 47 ± 8.4 , $p = 0.0257$), without differences between SUDD and PD ($p = 0.3009$). Regarding mental component

Table 3. Clinical features and lifestyle factors in diverticulosis, symptomatic uncomplicated diverticular disease and previous diverticulitis patients: adjusted logistic regression analysis.

| % | Diverticulosis <i>n</i> = 705 | SUDD <i>n</i> = 300 | PD <i>n</i> = 212 | OR (95% CI) ^a | OR (95% CI) ^b | OR (95% CI) ^c |
|--|----------------------------------|------------------------|----------------------|--------------------------|----------------------------|---------------------------|
| Female gender | 39 | 58 | 50.5 | 1.94 (1.43–2.62) | 1.79 (1.24–2.56) | 0.97 (0.64–1.48) |
| Age ≤ 60 years | 21 | 24.6 | 36.5 | 1.31 (0.92–1.86) | 2.10 (1.42–3.08) | 1.57 (1.01–2.45) |
| BMI ≥ 30 kg/m ² | 16.8 | 16.4 | 12.4 | 0.90 (0.61–1.33) | 0.63 (0.38–1.06) | 0.75 (0.42–1.32) |
| History of diverticular bleeding | 0.6 | 1 | 4.2 | 1.89 (0.31–11.70) | 29.29 (8.17–104.98) | 16.84 (3.77–75.25) |
| Family history for colonic cancer | 16.5 | 13.4 | 11 | 0.71 (0.47–1.08) | 0.58 (0.34–1.08) | 0.78 (0.42–1.43) |
| Family history for colonic diverticula | 18.4 | 21.7 | 28.7 | 1.15 (0.80–1.65) | 1.88 (1.27–2.78) | 1.54 (0.97–2.41) |
| Charlson index score ≥ 3 | 15.3 | 13.6 | 12.3 | 0.84 (0.56–1.28) | 0.83 (0.49–1.40) | 0.99 (0.54–1.80) |
| Active smoking | 14.8 | 12.5 | 20.1 | 0.79 (0.51–1.22) | 1.25 (0.79–1.97) | 1.61(0.94–2.76) |
| Use of alcohol | 40.1 | 33.4 | 40.2 | 0.88 (0.64–1.20) | 1.23 (0.85–1.78) | 1.42 (0.93–2.18) |
| Use of coffee | 80.3 | 80.1 | 78.9 | 0.98 (0.68–1.42) | 0.87 (0.56–1.36) | 0.75 (0.46–1.23) |
| Physical activity | 36.7 | 33.4 | 41.1 | 0.84 (0.61–1.14) | 1.12 (0.79–1.59) | 1.23 (0.81–1.86) |
| Diet rich in fibre | 57 | 61.3 | 56.6 | 1.15 (0.85–1.55) | 1.10 (0.77–1.58) | 0.90 (0.60–1.35) |

BMI: body mass index; CI: confidence interval; OR: odds ratio; SUDD: symptomatic uncomplicated diverticular disease; PD: previous diverticulitis. Data were presented as percentage of total.

^aDiverticulosis vs SUDD. ^bDiverticulosis vs PD. ^cSUDD vs PD.

**Figure 1.** Age distribution in diverticulosis, symptomatic uncomplicated diverticular disease (SUDD) and previous diverticulitis (PD) patients.

*Diverticulosis vs SUDD. **Diverticulosis vs PD patients. ***SUDD vs PD.

≤49 years: ***p* = 0.002; ****p* = 0.005.

50-59 years: ***p* = 0.003.

60-69 years: ***p* = 0.04.

70-79 years: ***p* = 0.02.

summary scores, patients with diverticulosis feel mentally better in comparison to SUDD (48.2 ± 9.6 vs 45 ± 10.1 , $p < 0.0001$) and PD (48.2 ± 9.6 vs 45.9 ± 9.9 , $p = 0.0038$), without differences between SUDD and PD scores ($p = 0.3544$). When subgroups are compared by the Kruskal–Wallis test, a significant difference is shown for physical ($p = 0.000024$) and mental scores ($p = 0.000005$).

Discussion

The REMAD Registry is the first prospective, nationwide, observational study which enrolled a cohort of consecutive patients with diverticulosis and DD. We aimed to compare patients with diverticulosis, SUDD and PD to ascertain whether demographic, clinical characteristics and lifestyle factors were associated to each subgroup of patients.

We showed that female gender was significantly associated with SUDD and PD compared to diverticulosis patients (OR 1.94 and OR 1.79). Regarding female prevalence in PD patients, this trend has been observed in other studies, belonging mainly to a national database on hospital admissions. Data from the United States of America (USA) showed that prevalence estimates for diverticulitis were higher for women

compared to men (98.6 vs 76.3/100,000),⁸ and similarly in England, the admission rate among females was higher than that among males.¹⁶ On the other hand, the association between female gender and symptoms associated to diverticula has been already observed in a case-control study. Indeed, only female patients, but not male, presented a positive association with diarrhoea (OR 1.39) and loose stools (OR 1.28).¹⁷

We observed that PD patients were younger in comparison to those without. Age ≤ 60 years was significantly associated with PD compared both to diverticulosis (OR 2.10) and SUDD (OR 1.57). This trend is in line with previous US epidemiological data, in which admission for DD is increasing, affecting mostly younger patients.^{7,18} Similarly in the United Kingdom, admissions younger than 50 years increased from 8% in 1995 to 42% in 2003 ($p=0.005$).¹⁹ Altogether these data, even from different epidemiological sources, suggest that younger age is frequently associated to diverticulitis.

The present study showed that females were significantly older in comparison to males in SUDD and PD subgroups, according to data belonging to epidemiological studies, where higher a prevalence of diverticulitis in women was found above age 45 years.^{8,16} This gender and age predominance in SUDD and PD does not have a conclusive explanation, and it might result from differences in risk factors between men and women.

This study highlighted for the first time the strong association between history of diverticular bleeding in PD patients compared to diverticulosis (OR 29.29) and SUDD (OR 16.84). This finding was unexpected since bleeding has been considered unrelated to other complications.^{1,20} Two earlier studies reported that bleeding occurs in up to 30% of diverticulitis;^{21,22} in this study we observed a concomitant episode of diverticular bleeding and diverticulitis in 4.2% of PD patients. However, our data should be considered with caution since past episodes of diverticular bleeding were sometimes anamnestic, not excluding a possible bias in reporting them. Further studies are needed to clarify this association and the possible shared risk factors associated to both conditions.

Another peculiar result is that PD patients more often presented a family history of colonic diverticula, compared to diverticulosis patients (OR 1.88). The contribution of hereditary factors to the development of diverticula has been reported.^{23,24} In a population-based study of twins and siblings, the relative risk RR was particularly strong in siblings of hospitalised cases (OR 4.11) and cases that underwent surgery (OR 5.37).²⁴ These observations substantially overlap with our findings, since an association between family history of diverticula and PD has been observed.

However, we cannot exclude that patients who have had an episode of diverticulitis may be more aware of this condition as other family members are affected, increasing the prevalence of colonic diverticula which otherwise might have gone unreported.

A recent systematic review and meta-analysis showed that an increase in BMI may increase the risk of diverticulitis.²⁵ Furthermore, a prospective cohort of male health professionals showed that men with a BMI ≥ 30 kg/m² had an RR of 1.78 for diverticulitis.²⁶ Our study did not show differences regarding the association of obesity with any subgroup of patients. In addition, when we analysed separately prevalence of BMI ≥ 25 or ≥ 30 kg/m² in men, or in patients with recent diverticulitis (<4 months), no differences emerged in the three subgroups (data not shown). We believe that our results are hard to compare with previous data obtained in prospective studies, since these data reflected a cross-sectional view and couldn't determine a diverticulitis risk.

Regarding lifestyle factors, a recent systematic review and meta-analysis showed that smoking increases the risk of developing diverticulosis and diverticulitis together (DD) with an RR of 1.36 for active smokers.²⁷ In our study, although we found a significant association between PD and active smoking compared to SUDD patients ($p=0.02$), this was not confirmed by logistic regression analysis. We have no clear explanation for this discrepancy but the weak RR observed in the cited meta-analysis suggested that smoking habit deserves more accurate studies.²⁷

A recent systematic review and meta-analysis investigated physical activity as a risk factor associated to DD, indicating that vigorous or high physical activity protects from DD.²⁵ Our study didn't find significant differences regarding physical activity in the subgroups of patients; however, these data should be considered with caution since we were able to evaluate only whether patients performed or did not perform regular physical activity.

Data regarding alcohol consumption and DD showed discordant findings, with some studies showing a positive association^{28,29} and others not.¹¹ Our study didn't find any association suggesting that the link between alcohol and DD should be better investigated. In addition, our study didn't find any association between coffee drinking and subgroups of patients, similarly to previously reported.²⁸

Regarding dietary habits, we have considered the consumption of a diet rich in fibre, without finding significant differences among subgroups of patients. Previous published data demonstrated that vegetarians and people who consume high-fibre diets may have a lower risk of diverticulitis;¹¹ consequently, we would expect that PD individuals would have a lower

consumption of dietary fibre. We cannot exclude that this lack of association belongs to the cross-sectional nature of the study, which gives a picture of the dietary habits of the population. It must also be pointed out that many physicians still advise patients to avoid high-residue foods based on the idea that these particles might damage a diverticulum, thereby initiating a cascade of events resulting in complications.³⁰ However, a large prospective study demonstrated that the consumption of these foods didn't increase the risk of complications, suggesting that this recommendation should be reconsidered.³¹ Our results probably reflected the current dietary habits in Italy, which may be influenced by patient beliefs, often on the basis of prior negative experience or because they are afraid of developing complications.³²

Finally, we observed that QoL scores were significantly higher in asymptomatic diverticulosis in comparison to SUDD and PD patients, without a difference between the last two subgroups. Different reports described the negative impact of diverticula on QoL, comparing patients with diverticula and those without.^{33,34} It is plausible that patients with DD, both SUDD and PD, because of their abdominal complaints or past complications, felt physically and mentally worse, differently from asymptomatic patients. It is of note that SUDD patients, complaining of chronic and troublesome abdominal symptoms, felt similarly to PD, suggesting that even an uncomplicated condition is considered a full disease justifying the broad therapeutic regimen used.³⁵⁻³⁷ The link between mental health and symptoms can be interpreted as either cause or effect but the fact that this is similar for SUDD and PD, where it could be assumed there is less influence of mental state on causation, suggested the disease might itself be causing some of the mental health decline. Indeed, the female prevalence in SUDD and PD might have affected these results. Abdominal complaints in patients with DD may overlap with IBS, and about 10% to 15% of DD patients meet the Rome Criteria for IBS diagnosis.^{2,3} It has been reported that DD and IBS patients present higher scores of somatisation when compared to healthy volunteers and asymptomatic diverticulosis, suggesting that these two conditions have a significant impact on patients' behaviour.³⁸ The current study was designed to assess clinical features and lifestyle factors associated to subgroups of DD patients, but is not able to focus on the possible overlap between IBS and SUDD. This study did not address how many patients meet the Rome Criteria for IBS diagnosis, not assessing whether symptoms might affect QoL, and this represents a limit for the interpretation of our data. Even if some clinical features have been reported to differentiate subgroups of DD patients, the reliable differential diagnosis between

these two conditions still remains challenging and should be addressed by ad hoc studies.

Another limit of this study was that a mean of 24% of patients did not adhere to the study, so data from this survey might not be perfectly representative, but we think that this exclusion rate should be acceptable, not representing a substantial bias of the findings. Moreover, since almost half of the cohort received a diagnosis of colonic diverticula in the absence of symptoms, with just a third complaining of abdominal pain, we believe that these proportions follow the clinical characteristics of DD, giving a representative picture of the Italian population.

In conclusion, this nationwide registry study showed that patients with past diverticular bleeding and family history of colonic diverticula are more prevalent in PD, representing a potential useful culprit in complicated diverticular disease. These two clinical anamnestic remarks, associated to the perceived worse QoL, should be kept in mind in the management of DD, including its therapeutic regimens.

Acknowledgements

REMAD Group collaborators and co-authors: Angelo Andriulli, San Giovanni Rotondo; Marco Asteggiano, Torino; Maria Pia Baldacci, Legnano; Marco Balzarini, Borgomanero; Stefano Bargiggia, Lecco; Gabrio Bassotti, Perugia; Maria Antonia Bianco, Torre del Greco; Gian Andrea Binda, Genova; Maria Erminia Bottiglieri, Marcianise; Carolina Ciacci, Salerno; Antonio Colecchia, Bologna; Marina De Matthaëis, Lavagna; Marco Dinelli, Monza; Virginia Festa, Roma; Davide Festi, Bologna; Luigi Gatta, Viareggio; Bastianello Germanà, Belluno; Mario Grassini, Asti; Ennio Guido, Padova; Andrea Laghi, Roma; Giovanni Latella, L'Aquila; Giovanni Maconi, Milano; Giampiero Manes, Garbagnate; Santino Marchi, Pisa; Riccardo Nascimbeni, Brescia; Matteo Neri, Chieti; Pietro Occhipinti, Novara; Marco Pennazio, Torino; Sergio Peralta, Palermo; Piero Portincasa, Bari; Marco Rossi, Arezzo; Raffaele Salerno, Milano; Vincenzo Savarino, Genova; Sergio Segato, Varese; Carola Severi, Roma; Giancarlo Spinzi, Como; Paolo Usai, Cagliari; Clara Virgilio, Catania.

Declaration of conflicting interests

Marilia Carabotti and Paolo Andreatti have nothing to declare.

Rosario Cuomo has served as a speaker and consultant for Alfa Wassermann, Allergan, Malesci, Almirall, Fresystem, Shire, Sofar, Biocure, Co.GE.DI, and Valeas, and has received research funding from Alfa Wassermann, Fresystem, Sofar, and CO.GE.DI.

Giovanni Barbara has served as a speaker and consultant for Alfa Wassermann, Allergan, Cadigroup, Danone, Ironwood, Italchimici, Malesci, Menarini, Noos, Shire, Synergy, Sofar, Yakult, and Zespri, and has received research funding from Alfa Wassermann, Cadigroup, Falk Pharma, IMA,

Italchimici, Lorenzatto, Parmalat Sofar, Yakult, and Zespri. Cesare Cremon has received consultancy fees and/or speaker fees from Alfa Wassermann, Almirall, Allergan, Valeas, and Sofar. Fabio Pace has served as a speaker for Allergan, Malesci, Menarini, and Alfa Wassermann.

Bruno Annibale has served as a speaker and consultant for Alfa Wassermann, Allergan, and Malesci, and has received research funding from Alfa Wassermann, Allergan, and Biohit.

Funding

This work was supported by unconditional funding by Alfa Wassermann.

Informed consent

All patients gave written informed consent to participate in this study.

Ethics approval

Ethical approval was granted at the coordinating centre for this study (University Federico II, Naples n. 161/14, 24 September 2014), after which local ethical approvals were obtained at the other participating centres. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

ORCID iD

Cesare Cremon  <http://orcid.org/0000-0002-7777-2936>.

References

- Stollman N and Raskin JB. Diverticular disease of the colon. *Lancet* 2004; 363: 631–639.
- Spiller R. Is it diverticular disease or is it irritable bowel syndrome? *Dig Dis* 2012; 30: 64–69.
- Cuomo R, Barbara G, Andreozzi P, et al. Symptom patterns can distinguish diverticular disease from irritable bowel syndrome. *Eur J Clin Invest* 2013; 43: 1147–1155.
- Annibale B, Lahner E, Maconi G, et al. Clinical features of symptomatic uncomplicated diverticular disease: A multicenter Italian survey. *Int J Colorectal Dis* 2012; 27: 1151–1159.
- Shahedi K, Fuller G, Bolus R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol* 2013; 11: 1609–1613.
- Strate LL, Modi R, Cohen E, et al. Diverticular disease as a chronic illness: Evolving epidemiologic and clinical insights. *Am J Gastroenterol* 2012; 107: 1486–1493.
- Etzioni DA, Mack TM, Beart RW Jr, et al. Diverticulitis in the United States: 1998–2005: Changing patterns of disease and treatment. *Ann Surg* 2009; 249: 210–217.
- Wheat CL and Strate LL. Trends in hospitalization for diverticulitis and diverticular bleeding in the United States from 2000 to 2010. *Clin Gastroenterol Hepatol* 2016; 14: 96–103.e1.
- Strate LL. Lifestyle factors and the course of diverticular disease. *Dig Dis* 2012; 30: 35–45.
- Peery AF, Barrett PR, Park D, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. *Gastroenterology* 2012; 142: 266–272.
- Crowe FL, Appleby PN, Allen NE, et al. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): Prospective study of British vegetarians and non-vegetarians. *BMJ* 2011; 343: d4131.
- Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40: 373–383.
- Ware J Jr, Kosinski M and Keller SD. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34: 220–233.
- Cuomo R, Barbara G, Pace F, et al. Italian consensus conference for colonic diverticulosis and diverticular disease. *United European Gastroenterol J* 2014; 2: 413–442.
- Barbara G, Scafoli E, Barbaro MR, et al. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. *Gut* 2017; 66: 1252–1261.
- Kang JY, Hoare J, Tinto A, et al. Diverticular disease of the colon – On the rise: A study of hospital admissions in England between 1989/1990 and 1999/2000. *Aliment Pharmacol Ther* 2003; 17: 1189–1195.
- Nagata N, Niikura R, Aoki T, et al. Association between colonic diverticulosis and bowel symptoms: A case-control study of 1629 Asian patients. *J Gastroenterol Hepatol* 2015; 30: 1252–1259.
- Bharucha AE, Parthasarathy G, Ditah I, et al. Temporal trends in the incidence and natural history of diverticulitis: A population-based study. *Am J Gastroenterol* 2015; 110: 1589–1596.
- Jeyarajah S and Papagrigoriadis S. Diverticular disease increases and effects younger ages: An epidemiological study of 10-year trends. *Int J Colorectal Dis* 2008; 23: 619–627.
- Niikura R, Nagata N, Shimbo T, et al. Natural history of bleeding risk in colonic diverticulosis patients: A long-term colonoscopy-based cohort study. *Aliment Pharmacol Ther* 2015; 41: 888–894.
- Mobley JE, Dockerty MB and Waugh JM. Bleeding in colonic diverticulitis. *Am J Surg* 1957; 94: 44–51.
- Wollaeger EE, Stauffer MH, Adson MA, et al. Massive hemorrhage from colonic diverticulitis. *Mayo Clin Proc* 1966; 41: 549–559.
- Granlund J, Svensson T, Olén O, et al. The genetic influence on diverticular disease – A twin study. *Aliment Pharmacol Ther* 2012; 35: 1103–1107.
- Strate LL, Erichsen R, Baron JA, et al. Heritability and familial aggregation of diverticular disease: A population-based study of twins and siblings. *Gastroenterology* 2013; 144: 736–742.
- Aune D, Sen A, Leitzmann MF, et al. Body mass index and physical activity and the risk of diverticular disease: A systematic review and meta-analysis of prospective studies. *Eur J Nutr* 2017; 56: 2423–2438.

26. Strate LL, Liu YL, Aldoori WH, et al. Obesity increases the risks of diverticulitis and diverticular bleeding. *Gastroenterology* 2009; 136: 115–122.
27. Aune D, Sen A, Leitzmann MF, et al. Tobacco smoking and the risk of diverticular disease – A systematic review and meta-analysis of prospective studies. *Colorectal Dis* 2017; 19: 621–633.
28. Aldoori WH, Giovannucci EL, Rimm EB, et al. A prospective study of alcohol, smoking, caffeine, and the risk of symptomatic diverticular disease in men. *Ann Epidemiol* 1995; 5: 221–228.
29. Tønnesen H, Engholm G and Moller H. Association between alcoholism and diverticulitis. *Br J Surg* 1999; 86: 1067–1068.
30. Peery AF and Sandler RS. Diverticular disease: Reconsidering conventional wisdom. *Clin Gastroenterol Hepatol* 2013; 11: 1532–1537.
31. Strate LL, Liu YL, Syngal S, et al. Nut, corn, and popcorn consumption and the incidence of diverticular disease. *JAMA* 2008; 300: 907–914.
32. Feinle-Bisset C and Azpiroz F. Dietary and lifestyle factors in functional dyspepsia. *Nat Rev Gastroenterol Hepatol* 2013; 10: 150–157.
33. Comparato G, Fanigliulo L, Aragona G, et al. Quality of life in uncomplicated symptomatic diverticular disease: Is it another good reason for treatment? *Dig Dis* 2007; 25: 252–259.
34. Bolster LT and Papagrigroriadis S. Diverticular disease has an impact on quality of life – Results of a preliminary study. *Colorectal Dis* 2003; 5: 320–323.
35. Bianchi M, Festa V, Moretti A, et al. Meta-analysis: Long-term therapy with rifaximin in the management of uncomplicated diverticular disease. *Aliment Pharmacol Ther* 2011; 33: 902–910.
36. Maconi G, Barbara G, Bosetti C, et al. Treatment of diverticular disease of the colon and prevention of acute diverticulitis: A systematic review. *Dis Colon Rectum* 2011; 54: 1326–1338.
37. Cuomo R, Barbara G and Annibale B. Rifaximin and diverticular disease: Position paper of the Italian Society of Gastroenterology (SIGE). *Dig Liver Dis* 2017; 49: 595–603.
38. Spiller RC, Humes DJ, Campbell E, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. *Aliment Pharmacol Ther* 2010; 32: 811–820.