






Sexual dysfunctions in inflammatory bowel disease: role of Mediterranean diet and quality of life

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Abstract

Background: Dietary factors and chronic gastrointestinal diseases are frequent determinants of sexual dysfunctions (SD). Whether inflammatory bowel diseases (IBD) are associated with SD is not well known as well as the role of diet and quality of life (QoL). **Objectives:** To evaluate the prevalence of SD in a cohort of IBD patients and assess the role of clinical-demographic variables, adherence to Mediterranean diet (MD) and QoL.

Materials and Methods: This is a cross-sectional observational study involving 301 patients (134 females and 167 males); 119 had Crohn's Disease and 182 had ulcerative colitis. SD were assessed through the Female Sexual Function Index (FSFI) and the International Index of Erectile Function (IIEF). Adherence to MD was evaluated by the MD Score. QoL was investigated by the 12-item Short-Form Health Survey (SF-12)

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which yields summary scores of physical (PCS) and mental (MCS) health. Multiple logistic regression was used to identify predictors of SD.

Results: Prevalence of SD in females was 61.9%, while 52.1% of males had erectile dysfunction. No differences in the prevalence of SD were found between CD and UC in both males and females. IBD activity, as defined by patient-reported outcomes, was significantly associated with SD in both sexes. In females, MD adherence score (OR 0.8, 95% CI 0.653–0.974, $p = 0.027$), PCS (OR = 0.936, CI 95% = 0.891–0.983, $p = 0.008$), and MCS (OR 0.9, 95% CI 0.906–0.985, $p = 0.008$) were protective against SD, whereas in males a higher PCS was associated with a lower probability of SD (OR 0.9, 95% CI 0.891–0.978, $p = 0.004$)

Discussion: IBD patients had a significant prevalence of SD which occurred more frequently in females than in males. Disease activity is associated with a higher likelihood of SD in both sexes, whereas dietary factors are differentially associated with SD in males and females. A better QoL is associated with a lower risk of SD.

Conclusion: SD is prevalent among men and women with IBD. Adherence to MD, PCS and MCS in females as well as PCS in males were protective against SD. The assessment of sexual function in IBD patients could be relevant in order to reach an early diagnosis and a timely treatment.

KEYWORDS

FSFI, IIEF, inflammatory bowel disease, Mediterranean diet, quality of life, sexual dysfunctions

1 | INTRODUCTION

Male and female sexual dysfunctions (SD) affect both physical and emotional well-being. The prevalence of women who report at least one SD is approximately 40–50% in the general population, irrespective of age.¹ On the other hand, the prevalence of erectile dysfunction (ED) increases with age, ranging from 1% to 10% in those younger than 40 years up to 50–100% for men in their 70s or 80s.¹ The Global Study of Sexual Attitudes and Behaviors, an international survey that included 13,882 females and 13,618 males aged 40–80 years old from 29 countries, reported that sexual disorders are strictly associated with physical health.² When associated with chronic comorbidities whose prevalence is increasing globally, SD can be considered systemic diseases leading to a decreased quality of life (QoL) and needing a multidisciplinary approach.³

Female sexual dysfunctions (FSD) are characterized by numerous disorders namely reduced sexual desire, arousal problems, inadequate lubrication, and pain during sex that negatively impact with females' quality of life, mental health, and relationships with their significant others.⁴ ED, which is defined by the inability to achieve or maintain an erection suitable for satisfactory sex, is an important medical symptom resulting from different etiologies, whose incidence and prevalence is associated with increasing age and presence of comorbidities.^{4,5} Both FSD and ED are related to unhealthy lifestyle habits, including diet, physical inactivity, smoking and alcohol abuse.^{6,7} Mediterranean diet (MD) is a healthy dietary pattern that has been

associated with an improvement of sexual function in both males and females.^{8–10}

The prevalence of SD has been found to be increased in a number of gastrointestinal (GI) disorders.¹¹ Recently, patients with celiac disease have been reported to experience an altered sexual function in a percentage higher than that seen in the general population.¹² Despite the increasing evidence of an altered sexual health in the setting of GI diseases, gastroenterologists seem to under-evaluate the problem of SD in their patients.¹³

Inflammatory bowel diseases (IBD) represent important, immune-mediated GI disorders with a chronic inflammation which may involve different sections of the GI tract and may also be associated to a number of extraintestinal manifestations, including the urogenital tract.¹⁴ The issue of SD has been investigated in patients with IBD [i.e., ulcerative colitis (UC) and Crohn's disease (CD)]. Most studies agree that patients with IBD have a higher prevalence of SD.^{14–17} However, differences between UC and CD have not been consistently evaluated and methods to assess SD are not univocal. Also, to our knowledge, the role of dietary patterns, and in particular the adherence to MD in this clinical setting has not been explored.

Therefore, this multicenter, observational, cross-sectional study was designed with the objective to evaluate (1) the prevalence of SD in patients with IBD; (2) the differences in the prevalence of SD between patients with CD and UC; (3) the clinical-demographic factors and their associations to SD in patients with IBD; and (4) the potential association of diet and QoL of IBD patients with SD.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This is a multicentric cross-sectional observational study involving patients attending the Gastroenterology and Endoscopy Units at University of Campania “Luigi Vanvitelli”, Naples, at University “Federico II”, Naples, at V. Monaldi Hospital, Naples, at G. Moscati Hospital, Avellino, and at V. Cervello Hospital, Palermo, Italy. The study was conducted from January 2023 to October 2023.

To be eligible for the enrollment in the study, participants had to be adults (18 years or older) with established IBD. We excluded from the study: legal unable patients to provide free consent for attendance, patients with diagnosed psychiatric disorders or already known sexual disorders. The following clinical-demographic variables were collected through an on-line questionnaire administered at the same time of those exploring MD, QoL and SD: age, gender, level of education, type of work, total number of partners, body mass index (BMI), smoking habits, consumption of alcohol, diagnosis of diabetes and/or, hypertension, type of IBD, duration of the disease, status of activity the disease, and ongoing biological therapy. The assessment of disease activity was based on the presence of symptoms related to the underlying IBD (i.e., urgency/frequency and abdominal pain for CD, and urgency/frequency and blood in the stools for UC) evaluated through the patients-reported outcomes.¹⁸ All participants completed the study questionnaires anonymously, considering sex stratification into males and females.

This study was conducted according to the principles of the World Medical Association Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. Furthermore, the study was approved by the Ethics Committee of University of Campania “Luigi Vanvitelli” (protocol n. 387/2022).

2.2 | Assessment of sexual dysfunction in the female population

Female patients completed the Female Sexual Function Index (FSFI), a validated questionnaire widely used in clinical practice.¹⁹ This questionnaire is made up of 19 questions, each of which is part of a domain exploring: sexual desire (questions 1 and 2, scores 1–5 and multiplication factor 0.6), sexual arousal (questions 3–6, scores 0–5 and multiplication factor 0.3), lubrication (questions 7–10, scores 0–5 and multiplication factor 0.3), orgasm (questions 11–13, scores 0–5 and multiplication factor 0.4), sexual satisfaction (questions 14–16, scores 0–5 and multiplication factor 0.4), and pain associated with sexual activity (questions 17–19, scores 0–5 and multiplication factor 0.4). Each domain has a minimum score (0 or 1.2) up to a maximum score of 6. Each domain’s score is multiplied by a correction coefficient, resulting in a domain subscore, which are all added to obtain the final score (from a minimum of 2 to a maximum score of 36). The cut-off limit considered to detect FSD was ≤ 26.5 .

2.3 | Assessment of sexual dysfunction in the male population

Male patients completed the 15-item International Index of Erectile Function (IIEF-15), a validated, multidimensional, self-administered questionnaire that investigates male sexual function in the last 4 weeks.²⁰ To each of the 15 questions is assigned a score from 0 to 5; they examine the main domains of male sexual function: erectile function (questions 1–5 and 15, total score 1–30), orgasmic function (questions 9 and 10, total score 0–10), sexual desire (questions 11 and 12, total score 2–10), relationship satisfaction (questions 6–8, total score 0–15) and overall satisfaction (questions 13 and 14, total score 2–10). Based on the results of the erectile function IIE (questions 1–5 and 15) we can classify erectile dysfunction as severe (first domain score: 6–10), moderate (11–16), mild (17–25) and absent (26–30). To define whether other aspects of male sexual function were compromised, we arbitrarily considered the value corresponding to the 83% of the total score for each of the remaining domains explored by IIEF-15 as a cut-off value.

2.4 | Assessment of adherence to Mediterranean diet

To evaluate the degree of adherence to the MD, the 9-point scale by Trichopoulou et al. was used.²¹ Each domain can be assigned a value of 0 or 1 as follows: about beneficial components (vegetables, legumes, fruit and nuts, cereals and fish) people whose consumption was below average received a score equal to 0, whereas people whose consumption was equal to or higher than the average received a score of 1. As for the presumed harmful components (meat, poultry, and dairy products) patients whose consumption was lower than the average, received a score equal to 1; people whose consumption was equal to or above average received a score of 0. For ethanol, a score of 1 was assigned to males who consumed between 10 and 50 g/day and to females who consumed between 5 and 25 g/day. Regarding fat intake, we used the ratio between monounsaturated lipids and saturated lipids. Therefore, the total score of the MD ranged from 0 to 9: patients with a score > 6 were stratified as people with “maximum adherence to the MD”, while those with a score ≤ 6 as people with “minimal adherence to the MD”.

2.5 | Assessment of Quality of Life

To investigate QoL of participants in the study, we used the SF-12 (Short Form Health Survey), a validated scale that allows to measure the physical and mental health status of respondents.²² It consists of a series of 12 Likert scale questions, each of which is designed to measure a specific aspect of physical health (physical activity, role limitations due to physical health, physical pain, general health) and mental health (vitality, social activities, emotional state, mental state, general health). Through appropriate statistical analysis techniques,²² the

information obtained from the individual questions is traced back to two synthetic numerical indices: the state of physical (PCS) and mental (MCS) health of people. The international reference values for these two synthetic indices are $50 + 10$ (Mean + Standard Deviation).

2.6 | Statistical Analysis

Descriptive statistics were used to present the data. The continuous variables were expressed as median and the interquartile (i.e., Q1 and Q3) range, and difference, while the discrete variables (ordinal and categorical) were expressed as number and percentage. The distribution of the variables was tested using the Kolmogorov–Smirnov test to assess their normality and to choose between parametric and non-parametric tests. Categorical variables were compared using the Chi-square test, if $\leq 20\%$ of expected cell counts are < 5 or the number of samples is at least 100, or Fisher's exact test if $> 20\%$ of expected cell counts are < 5 and the number of samples is less than 100, while the continuous and ordinal variables (discrete but sortable quantitative variables) were differentiated between groups (qualitative variables) and subgroups using the Mann–Whitney U test or the Kruskal–Wallis H test, depending on the degrees of freedom of the variable related to the group/subgroup. The strength of the correlation between two quantitative variables was examined using the Spearman correlation rho test. To identify predictive factors of SD, multivariate linear/logistic regression analysis was used, using FSFI-19 and IIEF-15 total score as dependent variables and illustrating the results as odds ratio (OR) with 95% confidence interval (CI). The p -value accepted as statistically significant was < 0.05 . A p -value < 0.01 was defined as highly significant. Data were recorded and statistically analyzed using the Statistical Package for Social Science software (IBM SPSS® Version 29.0.1.0 software—IBM Corp.).

The primary endpoint of the study was to estimate female and male SD prevalence in our sample of IBD patients, according to the features of the disease like activity status and duration. The secondary endpoint was to study how the clinical-demographic characteristics, adherence to the MD and the physical and mental health status (SF-12) of the patients are related to the scores obtained from the validated questionnaires used.

3 | RESULTS

3.1 | Clinical-demographic characteristics

A total number of 310 were eligible for the study. Nine patients (6 females and 3 males) refused to complete the questionnaires relative to sexual function and were excluded. Therefore, the final population included 301 patients, 167 males (55.5%) and 134 females (44.5%). The median age was 42 (IQR, 29–53, 24) years and the median BMI 23.7 (21.2–26.8, 5.6) kg/m^2 ; 90 patients (29.9%) were smokers, while 50 (16.6%) consumed alcohol. Thirteen patients (4.3%) had diabetes,

and 50 (16.6%) suffered from hypertension. One hundred and nineteen patients (39.5%) had Crohn's disease and 182 (60.5%) had ulcerative colitis; the median duration of the disease was 10 (4–16) years. 151 patients (50.2%) presented an active disease and, 207 (68.8%) were on therapy with a biological drug. Regarding the adherence to the MD, the general population had a median score of 4 (2–5), identifying 61 patients (20.3%) with maximum adherence. The physical health (PCS) and mental health (MCS) indices had a median score of 45.5 (38.1–53.9, 15.8) and 38.4 (30.2–48.1, 17.9) respectively, significantly lower than 50 (40–60, 20) that is the reference values for a healthy population.

Table 1 shows the clinical and demographic characteristics of participants in the study stratified by IBD. Age was slightly but significantly higher in UC patients versus CD patients ($p < 0.003$). Also, the MD score was significantly higher (i.e., higher adherence to MD) in UC versus CD patients ($p < 0.035$). Finally, a significantly higher number of CD patients were on biological therapy compared to UC patients ($p < 0.029$). No differences were found in the prevalence of disease activity as clinically assessed by asking patients if, at the time of questionnaire compilation, they had symptoms (i.e., diarrhea and abdominal pain in CD, diarrhea with blood, tenesmus, and urgency at defecation in UC). Among CD patients, 3 males and 5 females manifested perianal disease, all of whom had scores indicative of SD (data not shown).

3.2 | Sexual function in the female population

The median FSFI total score in our population of 134 females with IBD was 23.5 (16.7–28.9), with a prevalence of FSD of 83 females (61.9%). Specifically, identifying an index of altered FSFI subdomain as < 4.5 , we found that 96 females (71.6%) presented disorders of sexual desire, 94 (70.1%) of arousal, 78 (58.2%) of lubrication, 76 (56.7%) of orgasm, 62 (46.3%) of intercourse satisfaction, and 91 (67.9%) experienced sexual pain (data not shown).

Hypertension and IBD activity are significantly associated with low values of FSFI, indicative of altered sexual function (Supporting information, Appendix 1). No differences in the prevalence of SD were found between CD and UC.

At the univariate analysis, there were positive correlations between the MD adherence score ($r_{sp} = 0.267$, $p = 0.002$), PCS ($r_{sp} = 0.239$, $p = 0.006$) and MCS ($r_{sp} = 0.210$, $p = 0.015$) (data not shown). The distribution of SD and of physiological sexual function (NO SD) in relation to PCS, MCS, degree of adherence to the MD in the female study population is shown in Figure 1. At the multivariate logistic regression analysis (Figure 1), the MD adherence score (OR 0.8, 95% CI 0.653–0.974, $p = 0.027$), PCS (OR = 0.936, CI 95% = 0.891–0.983, $p = 0.008$) and MCS (OR 0.9, 95% CI 0.906–0.985, $p = 0.008$) were protective against SD (Supporting information, Appendix 2). Hypertension was significantly associated with low FSFI scores (i.e., altered sexual function) (OR 23.3, 95% CI 1.737–312.124, $p = 0.017$). There were no statistically significant associations between FSFI score and other considered clinical variables (Supporting information, Appendix 2).

TABLE 1 Clinical and demographic characteristics of the study population.

	Crohn's disease (N = 119)	Ulcerative colitis (N = 182)	p-value
Gender, n (%)			
Males	64 (53.8)	103 (56.6)	0.631
Females	55 (46.2)	79 (43.4)	
Age, years	37 (28–49, 21)	44 (32–55, 23)	0.003
Smoke, n (%)	39 (32.8)	51 (28)	0.352
Alcohol, n (%)	23 (19.3)	27 (14.8)	0.290
BMI, kg/m ²	23.4 (20.7–26.6, 5.9)	24 (21.6–27.1, 5.4)	0.107
Diabetes, n (%)	3 (2.5)	10 (5.5)	0.225
Hypertension, n (%)	17 (14.3)	33 (18.1)	0.415
Active disease, n (%)	61 (51.3)	90 (49.5)	0.759
Biological therapy, n (%)	90 (75.6)	121 (66.5)	0.035
Mediterranean diet score	3 (2–5, 3)	4 (3–5, 2)	0.029
PCS	45.2 (38–53.5, 15.5)	45.9 (38.2–54.3, 16.1)	0.748
MCS	38.4 (29.9–48.2, 18.3)	38.5 (30.6–47.3, 16.7)	0.806

Note: Data are expressed as median (IQR, difference) or number (percentage). Abbreviations: BMI, body mass index; MCS, mental score; PCS, physical score.

3.3 | Sexual function in the male population

The median IIEF-15 total score in the 167 males with IBD was 58 (41.5–67), with a prevalence of SD of 59.9% ($n = 100$ patients with IIEF-15 total score < 62). Specifically, according to the individual IIEF-15 subdomains, 87 males (52%) presented erectile dysfunction (score < 26), 67 (40.1%) orgasm disorders (score < 8), 98 (58.7%) sexual desire disorders (score < 8), 119 (71.3%) disorders of satisfaction during relationship (score < 12), 70 (41.9%) disorders of general satisfaction (score < 8) (data not shown).

Only IBD activity was significantly associated to altered IIEF-15 erection score ($p < 0.005$) (Supporting Information, Appendix 3). No differences in the prevalence of SD were found between CD and UC.

At univariate analysis, IIEF-15 was negatively associated with age ($r_{sp} = -0.189$, $p = 0.015$) and positively associated with the PCS physical health parameter ($r_{sp} = 0.248$, $p = 0.001$) (data not shown). Figure 2 shows the distribution of SD and physiological sexual function (NO SD) in relation to PCS and age in the male study population. At multivariate logistic regression analysis, we identified age as a significant, predictive, risk factor for SD (OR 1.05, 95% CI 1.017–1.082, $p = 0.003$) while PCS was significantly protective against SD (OR 0.9, 95% CI 0.891–0.978, $p = 0.004$) (Appendix 4). There were no statistically significant associations between IIEF-15 score and other considered clinical variables (Supporting information, Appendix 4).

4 | DISCUSSION

In this study we first sought to evaluate the prevalence of SD in patients with IBD and found that both females and males suffering from IBD had a high prevalence of SD as assessed by the FSFI-19 and IIEF-15

questionnaires. In detail, over 70% of females complained of disorders of sexual desire or arousal, and almost 68% of dyspareunia whereas the most preeminent complaints of males were ED (52%) and reduction of desire (59%). SD was significantly associated with clinical active disease and no significant differences were found between CD and UC.

The prevalence of SD found in this study (i.e., 61.9% in females and 59% in males) was higher than that reported in the general population which is approximately 40–50% for females, independently of age, and 1% to 15% in the age-matched male population.²³ This is in agreement with previous studies which found that IBD patients are at higher risk of experiencing SD.^{14,15,17} In particular, in a recent study of 208 IBD patients, Zhang et al. found a prevalence of FSD of 61.9% in females and a prevalence of ED of 43.5% compared with 24.4% and 12.4% in female and male controls, respectively.¹⁴

We did not find any significant difference in SD prevalence according to the underlying IBD (i.e., CD vs. UC). This confirms the evidence reported by Zhang et al.¹⁴ and Pires et al.¹⁷ who did not find significant differences in the prevalence of SD in people affected by CD and UC. However, differences in the prevalence of SD between CD and UC emerged in studies which more closely explored the individual disease characteristics, such as extension and activity, together with the specific domains of SD. In particular, a cross-sectional study which included a population-based cohort of Danish females showed that CD patients reported more frequent deep dyspareunia and difficulty in achieving orgasm than females with UC.²⁴ In this regard, perianal fistulas seem to be an important risk factor for SD among female CD patients.²⁵

The influence of disease duration as a risk factor for SD in IBD is a controversial issue. Muller et al. reported that patients of both sexes with a long duration of the disease (> 3 years) were 2.59 times more likely to have decreased libido.²⁶ However, a previous study showed that a disease duration > 10 years was not a determinant of low sexual

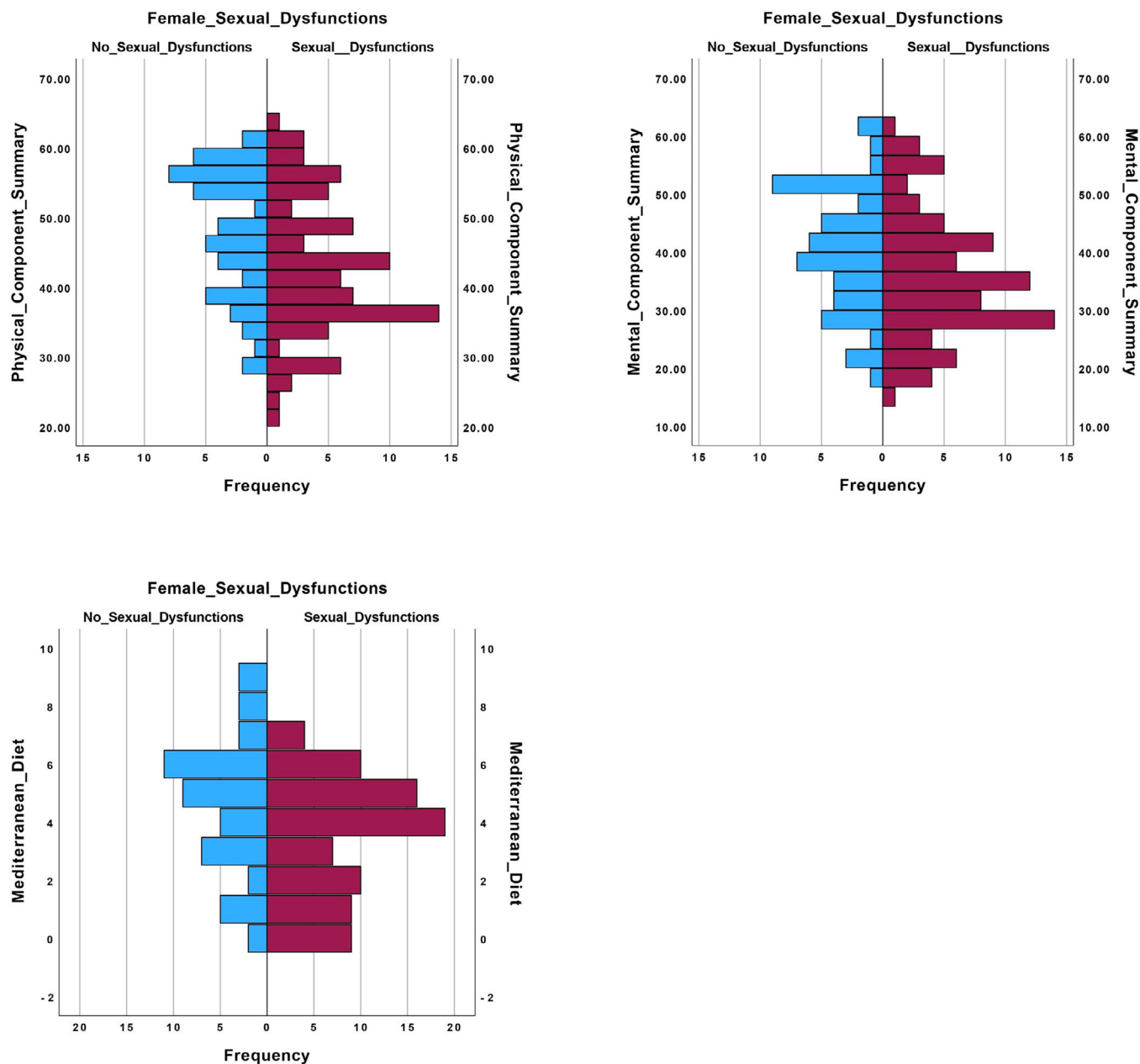


FIGURE 1 Distribution of sexual dysfunctions (SD) and physiological sexual function (NO SD) according to physical component summary (PCS), mental component summary (MCS), degree of adherence to the MD in the female study population.

function in females with IBD.²⁷ Our data are in line with Timmer et al.²⁷ showing no differences in SD prevalence in relation to disease duration.

In our study, disease activity, assessed through the evaluation of patients-reported outcomes [i.e., urgency/frequency and abdominal pain for CD, and urgency/frequency and blood in the stools for UC (19)], was a significant risk factor for SD in both sexes. This has been also confirmed by several studies which mainly considered activity of disease on the basis of symptoms-based scores.^{14,28,29} However, a recent study by Mules et al. did not find a significant association between SD and IBD disease activity,¹⁶ whose assessment was though based on endoscopic and serological indexes of inflammation rather than symptoms-based scores.

We also found that age in males and hypertension in females were risk factors for SD. Regardless of health status, age was recognized as an important risk factor for SD in males.³⁰ This has been confirmed even in recent observational studies of males with IBD, which identified age as a risk factor for ED.^{17,31} Moreover, a recent meta-analysis that included 8 studies reported that relatively younger IBD patients (males < 50 years, females < 40 years) had a higher risk of SD than those of older age. The authors attributed this result to the age of IBD diagnosis, which usually occurs between the ages of 15 and 35 and interferes the sexual function of people suffering from a chronic disease at an early stage.³² Moreover, although females with hypertension have been shown to have a higher risk of SD than the general

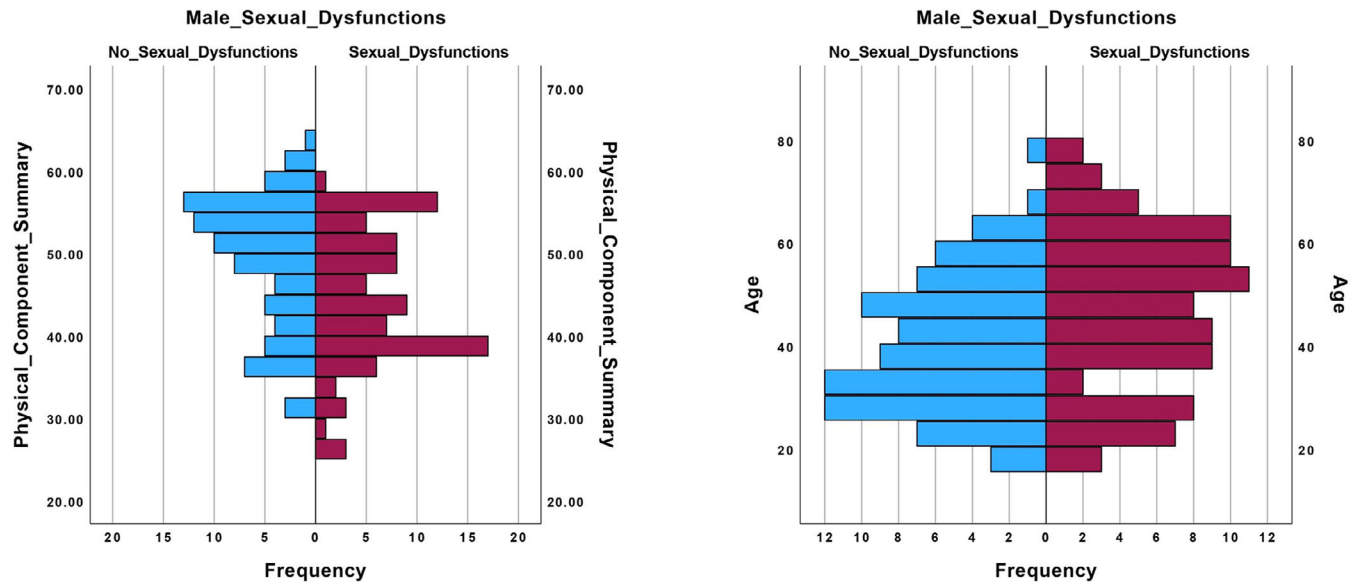


FIGURE 2 Distribution of sexual dysfunctions (SD) and physiological sexual function (NO SD) according to PCS and age in the male study population. Data are expressed as frequency.

population,^{30,33,34} the relationship between hypertension and FSD has never been investigated in the context of IBD. Our finding of a significant association between hypertension and FSD therefore needs to be confirmed in larger longitudinal studies.

Sexual dysfunction has a negative impact on quality of life and interpersonal relationships in both males and females. Our findings confirm that physical well-being is strictly related to satisfying sexual activity.³⁵ Indeed, sexual health should be used as a surrogate marker for systemic health facilitating the diagnosis, treatment and prevention of chronic diseases.³ It is also known that emotional and psychological factors play a prominent role as determinants of sexual function in females.³⁰ This concept is already included in the definition of FSD, which refers to multidimensional disorders involving physiological, clinical, psychological and sociocultural factors.⁴

We report for the first time that adherence to MD is protective against sexual dysfunctions in females with IBD but not in males. The gender difference related to the association linking MD to SD in patients suffering from IBD remains unclear. Since sexual function in women is strictly influenced by sociocultural factors, we could speculate that paying more attention to diet may reflect a specific attitude in remaining focused on healthy behaviors that are related also to sexual activity. The lack of any other study describing the effects of Mediterranean dietary pattern on IBD does not allow to make comparison. Further studies should clarify the relationship between diet and sexual function in people with IBD. However, there is evidence demonstrating beneficial effects of MD on sexual function in both males and females, and specifically in people affected by metabolic disorders.^{6–10}

There are several pathophysiological mechanisms underlying SD in IBD patients. In males, an increased prevalence of ED, especially in the elderly, could be due to hypogonadism which has been demonstrated to be frequently associated to IBD patients.^{31,36} In addition, IBD may be associated with endothelial dysfunction which, in turn, may contribute

to the development of ED.³⁷ through the loss of nitric oxide (NO)-dependent vasodilation, leading to decreased perfusion of the corpus cavernosum.³⁸ Moreover, in both males and females, IBD may have a negative impact on self-estimation, especially during the active phases of the disease, and in particular in subjects with perianal disease with formation of perianal fistulas or even fistulas between the intestinal and genital tract (i.e., enterovaginal fistulas). Finally, an inflammatory condition of the intestine might affect sexual function through cross-organ pelvic sensitization which refers to the ability of a given organ to influence the homeostasis of an adjacent or distant organ by the transmission of noxious stimuli.^{39,40} In partial support of this hypothesis, we have recently demonstrated and increased prevalence of lower urinary tract symptoms in patients with IBD.⁴¹

This study has its limitations. Due to its cross-sectional nature, no conclusions can be drawn about cause and effect. As with most epidemiological studies, there is the possibility of residual bias due to uncontrolled covariates. The major strengths of this study include the use of a validated instrument to assess sexual dysfunction, the large number of people studied, the comprehensive assessment of numerous aspects of life related to sexual function (quality of life, lifestyle habits) and IBD (activity status), and the analyses in both sexes.

SD are prevalent among patients with IBD and more frequent in females than in males with differences in their clinical predictors between sexes. Adherence to MD is protective against SD in females with IBD. Longitudinal studies are needed to confirm these findings on larger populations. In the meantime, the assessment of sexual function in IBD patients could be important for early diagnosis and timely treatment.

AUTHOR CONTRIBUTIONS

Lorenzo Romano, Mariano Fonticelli, Marco Romano, and Maria Ida Maiorino conceived the study and wrote the manuscript. Agnese

Miranda, Kateryna Priadko, Luigi Napolitano, Felice Crocetto, Biagio Barone, Davide Arcaniolo, Lorenzo Spirito, Celeste Manfredi, Antonietta Gerarda Gravina, Carmine Sciorio, Debora Compare, Raffaele Melina, Dolores Sgambato, Ambrogio Orlando, Silvia Calderone, Olga Maria Nardone, and Gerardo Nardone collected data and reviewed the manuscript for intellectual content. Paola Caruso, Katherine Esposito, and Marco De Sio contributed to the data analysis and in writing the manuscript. Lorenzo Romano and Mariano Fonticelli did the statistical analyses and contributed to the data analysis. All authors approved the final version of the manuscript. Marco Romano and Maria Ida Maiorino are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

How to cite this article: Romano L, Fonticelli M, Miranda A, et al. Sexual dysfunctions in inflammatory bowel disease: role of Mediterranean diet and quality of life. *Andrology*. 2024;1-9. <https://doi.org/10.1111/andr.13791>