Inflammatory Intestinal Diseases

Research Article

Inflamm Intest Dis
DOI: 10.1159/000534413

Received: July 19, 2023
Accepted: September 27, 2023
Published online: October 3, 2023

Lifestyle Factors and Silent Inflammatory Bowel Disease

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Keywords
Lifestyle factors · Silent inflammatory bowel disease · Abdominal pain

Abstract
Introduction: Hypoalgesic or silent inflammatory bowel disease (IBD) is a poorly understood condition that has been associated with poor clinical outcomes. There is evidence that lifestyle factors, including diet, exercise, and substance use can influence inflammatory activity and symptoms in IBD. It is unclear, though, whether these issues impact pain experience in IBD. We performed this study to evaluate the potential relationship between several key lifestyle factors and silent IBD. ***Methods:*** We performed a retrospective analysis using an IBD natural history registry based in a single tertiary care referral center. We compared demographic and clinical features in 2 patient cohorts defined using data from simultaneous pain surveys and ileocolonoscopy: (a) active IBD without pain (silent IBD) and (b) active IBD with pain. We also evaluated the relative incidence of characteristics related to diet, exercise, sexual activity, and substance abuse. ***Results:*** One hundred and eighty IBD patients had active disease and 69 (38.3%) exhibited silent IBD. Silent IBD patients exhibited incidences of disease type, location, and severity as pain-perceiving IBD patients. Silent IBD patients were more likely to be male and less likely to exhibit anxiety and/or depression or to use cannabis, analgesic medication, or corticosteroids. There were no significant differences in dietary, exercise-related, or sexual activities between silent and pain-perceiving IBD patients. ***Conclusions:*** Silent IBD was associated with reduced incidence of substance and analgesic medication use. No relationships were found between silent IBD and diet, exercise, or sexual activity, though specific elements of each require further dedicated study.

Introduction

When inflammatory bowel disease (IBD) patients with clinically significant disease activity do not simultaneously experience and/or report abdominal pain, they are described as having hypoalgesic or silent IBD. This is a relatively common phenomenon, affecting 25% or more of both Crohn's disease (CD) and ulcerative colitis (UC) patients [1]. Silent IBD is important because it has been associated with the development of more frequent and serious complications, including strictures, fistulae, and abscesses [2, 3]. As a result of these complications, silent IBD patients may require more intensive healthcare resources over time, including hospitalization [4].

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Silent IBD is challenging to manage, in part because so little is known about what causes this condition. Recent Investigations have provided clues regarding potential contributing variables, including age, sex, and (the lack of) comorbid psychiatric conditions [1]. There is even evidence for a potential genetic role in this condition [3]. However, much remains unknown about its underlying pathophysiology, and so IBD providers continue to struggle to identify at-risk patients. A more complete understanding of the causes and modifiers of silent IBD will be critical in order to more effectively screen for and manage it with this set of disorders.

Lifestyle factors may play an important role in this context. These include individual behaviors related to diet and nutritional status, physical activity, sexual activity, and substance use. Each of these variables been studied in the context of IBD and have exhibited at least potential to influence disease activity and other patient-related outcomes [5, 6]. For example, healthy dietary patterns (e.g., consumption of foods like fruits and vegetables even when asymptomatic and/or avoiding diets rich in processed proteins and/or carbohydrates) and having a normal body mass index (BMI) (e.g., 18.5–24.9 kg/m^2) appear to have positive effects on treatment efficacy, the course of IBD, and/or likelihood of experiencing IBD-associated symptoms [7–10]. Regular exercise has also previously been associated with several positive outcomes, including reduction of IBD-related disease activity and improvement in the severity or frequency of some symptoms (e.g., fatigue), particularly in the setting of quiescent disease [11, 12]. Substance use has also been implicated as a potentially important variable in this context. There is evidence that alcohol, tobacco, and narcotic use can increase the risk of flares and associated symptoms in IBD, including pain [13, 14]. However, no studies have yet been undertaken to specifically evaluate the relationship between lifestyle factors and silent IBD.

Our primary aim in undertaking this study was to evaluate for potential associations between silent IBD and specific lifestyle factors (including dietary behavior, physical activity, substance use, and sexual activity). We compared these characteristics in two carefully phenotyped groups: a cohort of silent IBD patients and IBD patients with active disease exhibiting abdominal pain.

Methods

Study Population

We performed a retrospective analysis using information derived from the Intestinal Diseases Natural History Database and Gastrointestinal Data Registry at our institution between January 1, 2017 and August 31, 2021. These databases include clinical and research information related to the encounters of IBD patients receiving clinical management at a tertiary care referral hospital with a dedicated IBD center that cares for over 5,000 patients with IBD. Written informed consent was obtained from each participant and all of this work was performed in accordance with the rules and regulations set forth by Penn State College of Medicine Institutional Review Board, approved under protocol STUDY00017310.

In order to be included in this study, participants had to be adults (i.e., greater than 17 years of age) and have an established diagnosis of CD or UC, based upon standard clinical criteria routinely used to identify IBD [15]. They also needed to have undergone an ileocolonoscopy and completed contemporaneous surveys on abdominal pain experience (including the Short Inflammatory Bowel Disease Questionnaire [SIBDQ] and Harvey-Bradshaw Index [HBI] or Short Colitis Activity Index [SCCAI]), as well as surveys related to dietary patterns, exercise, sexual activity, and substance use.

UC patients were excluded if they had undergone previous IBD-related colonic surgery. Of note, individuals who were pregnant, had colitis of indeterminate nature, and/or a current diagnosis of a gastrointestinal infection, cancer, endometriosis, pancreatitis, symptomatic cholelithiasis, or other potential extraluminal causes of abdominal pain were excluded from this study.

Definitions and Data Abstraction

"Significant inflammation" was defined as moderate to severe activity based upon findings during endoscopic evaluation (UC: using a Mayo endoscopy sub-score ranging from 0 to 3, with 0 = no disease ["quiescent"], 1 = mild disease, 2 = moderate disease, and 3 = severe disease; CD: using SES-CD scores of 7–15 for moderate disease and >15 for severe disease) and histopathological evaluation (hematoxylin and eosin sections were blindly assigned an inflammatory score by a trained pathologist specializing in digestive disease). Of note, all individuals included in this study had undergone previous endoscopic and radiologic testing, and IBD location and type was based upon the findings of those tests. All determinations about inflammatory state were based upon direct endoscopic evaluation of the mucosa and histologic assessment of tissue biopsies taken in areas of previously established disease activity. This information was used to make the most objective assessment of current gastrointestinal inflammatory status possible.

The determination of the presence of abdominal pain in each case was based on responses to two separate questions answered on the day of ileocolonoscopy: (1) the fourth question in the SIBDQ ("How often over the past 2 weeks have you experienced abdominal pain?", where patients respond using a frequency-based inverse Likert scale, with 1 representing pain "all of the time" and 7 representing pain "none of the time") and (2) the second item from the HBI which assess current severity of abdominal pain and includes potential responses of 0 ("no abdominal pain"), 1 ("mild"), 2 ("moderate"), and 3 ("severe"). For the purposes of this study, clinically relevant abdominal pain was defined as a numeric rating of <6 on the SIBDQ pain score *and* a score of 1 or greater on the HBI pain score. Patients were asked to focus on abdominal pain experience unrelated to symptoms they may have experienced in the setting of their respective bowel preps. Additionally, no study participants had a history of or demonstrated objective

evidence of extra-luminal causes of abdominal pain (including pancreatitis, symptomatic cholelithiasis, or endometriosis) based upon the most recent laboratory and imaging studies or clinical evaluation.

Dietary behavior was assessed by asking study participants, "How many times per day do you normally eat?" (with potential responses including (a) less than one meal per day, (b) one meal a day, (c) two meals a day, (d) three meals a day, (e) more than three meals a day). We compared the proportions of study participants who reported three or more meals per day to those reporting consumption of less than three meals a day between the hyperalgesic IBD and non-hyperalgesic IBD cohorts. Nutritional status was assessed by evaluating the mean BMI (kg/m^2) and serum albumin level (g/dL) of the two cohorts above. Incidence of BMI outside of the "normal" range (18.5–24.9 kg/m^2) was also compared between these cohorts. Recent physical activity levels were evaluated by asking the question, "How many times per week do you exercise?" and "How long (in minutes) do you exercise per week?". The proportions of individuals who reported exercising three or more times per week to those exercising less than 3 times per week were compared between hyperalgesic and non-hyperalgesic IBD patients. The mean time engaged in exercise each week was also compared between these cohorts. Of note, we also compared the proportions of individuals who reported undertaking 150 min of exercise per week (the minimum amount of time for adults to exercise each week recommended by the Centers for Disease Control [cdc.gov]) in both of these cohorts, but there were only four total individuals (hyperalgesic = 3 [3.2%] versus non-hyperalgesic = 1 [1.2%], $p = 0.62$) who met this criterion, so we opted against reporting this particular analysis below. Sexual activity was evaluated based upon responses to the question, "In the past month, how many times have you been sexually active?" Participant responses were dichotomized to compare individuals reporting to have sex once or more in the past month to those reporting no sexual activity in the last month. Finally, substance use was evaluated using the following questions: (a) "Over the past week, have you smoked or vaped tobacco?", (b) "Over the past week, how many alcoholic drinks have you consumed?", (c) "Over the past week, have you used any of the following substances and, if so, how many times have you used them: (1) cannabis/marijuana, (2) cocaine, (3) methamphetamine, (4) heroin/non-prescription opioid?". As relatively few study participants reported use of cocaine, methamphetamine, or heroin/non-prescription opioids, we combined all of them into the category described as "illicit substance use" and evaluated their use together. Finally, current prescription opioid use was also assessed. Responses were dichotomized based upon any reported use of a particular substance or no use at all. Of note, in the state of Pennsylvania (where our institution is located), there are no specific restrictions related to opioid prescription in the context of IBD. IBD patients are also eligible to receive medicinal marijuana.

In addition to the information outlined above, other clinical and demographic data were abstracted from the electronic medical record. Specifically, age, gender, IBD duration, IBD extent/location (e.g., organ involvement, using the Montreal classification system), disease complications (including intestinal stricture and intra-abdominal fistula), extra intestinal manifestations (EIMs) (including inflammatory arthritides, IBD-associated dermatopathies [including pyoderma gangrenosum], erythema nodosum, uveitis, episcleritis, and primary sclerosing cholangitis), medication use (including antidepressant/anxiolytic, corticosteroid, mesalamine, immunomodulator [azathioprine, 6-mercaptopurine, and/or methotrexate], and biologic therapy [infliximab, adalimumab, certolizumab, golimumab, vedolizumab, and/or ustekinumab]), IBD surgery history, laboratory values (white blood cell count [WBC], sedimentation rate [ESR], C-reactive protein [CRP]), "other" pain medication use (acetaminophen, NSAIDs, dicyclomine and/or tricyclic agents) were abstracted. Presence of anxiety or depression symptoms was determined based upon responses to the Hospital Anxiety and Depression Scale (HADS) completed at the time of the clinical encounter, using anxiety or depression subscores of 8 or greater to indicate the clinically significant presence of each [16].

Statistical Analysis

Data were extracted and analyzed using GraphPad Prism version 8 (San Diego, CA, USA) or R 4.2.0 (R Core Team (2022). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org.). Initially, summary statistics were computed for the whole study cohort and then for the following sub-cohorts: (1) IBD patients with active disease with no abdominal pain (hereafter referred to as "ANP-IBD") and (2) IBD patients with active disease with abdominal pain (hereafter referred to as "AP-IBD"). Bivariate analysis (e.g., two sample Student's t test, χ^2 test, or Fisher's exact test as appropriate) was also performed to compare demographic and clinical variables for the ANP-IBD and AP-IBD sub-cohorts. A multivariable logistic regression model was then performed incorporating each significant variable ($\alpha = 0.05$) identified during the univariate analysis, along with three other variables that had previously been associated with hypoalgesia in IBD [1] to examine the odds of developing ANP-IBD. The primary endpoint for each of these analyses was ANP-IBD (as defined above). Values listed represent means +/− standard error measurement, percentages or odds ratio with 95% confidence intervals unless indicated otherwise.

Results

Clinical and Demographic Characteristics of the Study Cohorts

We included 180 consecutive IBD patients (85 females and 95 males) with moderate to severe luminal inflammation (i.e., Mayo endoscopy sub-score of 2–3 or SES-CD of 7 or greater) who had undergone an ileocolonoscopy and completed concomitant pain-related surveys at our center (Table 1). One hundred and eleven individuals had CD (22.5% ileal CD [L1], 22.5% colonic CD [L2], 55.0% ileo-colonic CD [L3]) and 69 had UC (5.8% had proctitis, 26.1% L-sided UC, 68.1% pan-UC). In this cohort, 69 patients (38.3%) were found to have silent IBD (ANP-IBD). Similar rates of silent IBD (37.8 vs. 39.1%, $p = 0.88$) were exhibited in CD and UC. Due to this finding and the relatively small size of the study cohort and CD/UC sub-cohorts, we decided not to evaluate for other differences between IBD sub-types in this setting.

Table 1. Demographic and clinical characteristics of silent and pain-perceptive IBD cohorts

Variable	Cohort	Silent IBD (ANP-IBD)	Pain-perceptive IBD (AP-IBD)	*p* value
Sample (% female)	180 (47.2%)	**69 (30.4%)**	**111 (57.7%)**	**0.0004**
Age, years	42.7±1.2	44.7±2.1	41.5±1.4	0.186
Disease type	CD-111	42	69	
	UC-69	27	42	0.876
Disease duration, years	11.3±0.8	11.2±1.2	11.4±1.0	0.925
Stricturing (CD)	72	30 (71.4%)	42 (60.9%)	0.308
Non-perianal Fistula(e) (CD)	32	16 (38.1%)	16 (23.2%)	0.082
Severe inflammation (endoscopy)	50	19 (27.5%)	31 (27.9%)	0.999
Prior IBD-related surgery	44	15 (21.7%)	29 (26.1%)	0.551
EIM ever	92	**28 (40.6%)**	**70 (63.1%)**	**0.004**
SIBDQ	45.7±1.1	**57.5±1.2**	**38.3±1.2**	**<0.0001**
Harvey-Bradshaw Index	7.5±0.5	**4.5±0.9**	**9.4±0.6**	**<0.0001**
Short clinical colitis activity index	4.5±0.3	**2.3±0.3**	**5.9±0.3**	**<0.0001**
Laboratory studies				
WBC, 10^3 cells/mm^3	8.7±0.3	8.4±0.4	8.9±0.4	0.411
ESR, mm/h	21.1±1.8	21.4±2.7	21.0±2.0	0.921
CRP, mg/dL	0.9±0.2	1.7±0.4	2.0±0.3	0.581
Active IBD medication use				
Corticosteroid	24	**3 (4.3%)**	**21 (18.9%)**	**0.006**
Mesalamine	36	**23 (33.3%)**	**13 (11.7%)**	**0.0009**
Immunomodulator	4	18 (26.1%)	28 (25.2%)	0.999
Biologic	111	39 (56.5%)	72 (64.9%)	0.274
Symptoms of anxiety/depression	86	**15 (21.7%)**	**71 (64.0%)**	**<0.0001**
Antidepressant/anxiolytic use	41	**8 (11.6%)**	**33 (29.7%)**	**0.006**

Quantitative parameters are expressed as mean ± SEM, and qualitative parameters are shown as *n* (%). Bold indicates variables that demonstrated statistically significant differences between the cohorts. EIM, extra-intestinal manifestation; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; ESR, sedimentation rate; CRP=C-reactive protein.

Patient age (44.7 vs. 41.5 years, $p = 0.18$), disease duration (11.2 years vs. 11.4 years, $p = 0.92$), and disease location (CD: L1 16.7 vs. 26.1%, L2 21.4 vs. 23.2%, L3 61.9 vs. 50.7% [$p = 0.44$]; UC: E1 0.0 vs 2.5%, E2 23.5 vs 32.5%, E3 76.5 vs 65.0% [$p = 0.50$]) were statistically similar between the silent and pain-perceptive sub-cohorts, respectively. However, silent IBD patients were more likely to be male (69.6 vs. 42.3%, $p = 0.0004$).

Silent IBD and pain-perceptive patients had very similar proportions of severe endoscopic scores (27.5 vs. 27.9%, $p = 0.99$) and inflammatory laboratory values, including WBC (8,372 cells/mm^3 vs. 8,858 cells/mm^3, $p = 0.41$), CRP (1.7 mg/dL vs. 2.0 mg/dL, $p = 0.58$), and ESR (21.4 mm/h vs. 21.0 mm/h, $p = 0.92$). Silent CD patients and pain perceptive CD patients exhibited similar rates of previous IBD-associated surgeries (21.7 v. 26.1%, $p = 0.55$). Silent IBD patients had a higher mean SIBDQ (57.5 vs. 38.3, $p < 0.0001$) and lower mean HBI (4.5 vs. 9.4, $p < 0.0001$) and SCCAI (2.3 vs. 5.9, $p < 0.0001$). Silent IBD patients were less likely to exhibit extra-intestinal manifestations (40.6 vs. 63.1%, $p = 0.004$) and were also less likely to exhibit clinically significant symptoms of anxiety or depression (21.7 vs. 64.0%, $p < 0.0001$) or to use antidepressant or anxiolytic medications (11.6 vs. 29.7%, $p = 0.006$). Of note, rates of stricture in CD patients were statistically similar between the cohorts (75.0 vs. 61.8%, $p = 0.21$), but silent CD patients trended toward having a higher rate of intra-abdominal fistulae than their pain-reporting counterparts (38.1 vs. 23.2%, $p = 0.08$). Current corticosteroid (4.3 vs. 18.9%, $p = 0.006$) and mesalamine (33.3 vs. 11.7%, $p = 0.001$) use were significantly different between the silent and pain-perceptive cohorts. However, use of immunomodulator (26.1 vs. 25.2%, $p = 0.99$) and biologic medications (56.5 vs. 64.9%, $p = 0.27$) were each statistically similar between these cohorts. No other overt differences in demographics or clinical characteristics were identified.

Lifestyle Factors in the Silent and Pain Perceptive IBD Cohorts

Dietary Behavior and Nutritional Status

Mean BMI (kg/m^2) (25.2 vs. 30.1, $p = 0.18$) and mean albumin (g/dL) (3.9 vs. 3.9, $p = 0.90$) were not significantly different between the silent and pain-perceptive cohorts (Table 2). The proportion of individuals with an

Table 2. Lifestyle factors in the silent and pain-perceptive IBD cohorts

Variable	Cohort	Silent IBD (ANP-IBD)	Pain-perceptive IBD (AP-IBD)	*p* value
Dietary and nutritional assessment				
Eating 3+ meals per day	99	43 (62.3%)	56 (50.5%)	0.127
BMI	28.4±1.8	25.2±1.1	30.1±2.6	0.180
Abnormal BMI	51	18 (26.1%)	33 (29.7%)	0.999
Albumin, g/dL	3.9±0.1	3.9±0.2	3.9±0.1	0.901
Exercise				
Exercise sessions per week	2.6±0.2	2.8±0.3	2.4±0.2	0.318
Time exercising per week, min	31.5±4.3	36.2±8.3	28.6±4.7	0.389
Exercising 3+ times per week	93	38 (55.1%)	55 (49.5%)	0.540
Sexual activity				
Number of times had sex last month	3.0±0.4	3.5±0.7	2.7±0.4	0.335
Sexually active 1+ time last month	108	47 (68.1%)	76 (68.4%)	0.999
Active substance/pain medication use				
Tobacco	26	9 (13.0%)	17 (15.3%)	0.828
Alcohol	58	28 (40.6%)	30 (27.0%)	0.072
Cannabis	13	**1 (1.4%)**	**12 (10.8%)**	**0.012**
Opioid	13	3 (4.3%)	10 (9.0%)	0.375
Illicit substance(s)	13	4 (5.8%)	6 (5.4%)	0.999
Other pain meds	64	**17 (24.6%)**	**47 (42.3%)**	**0.017**

Quantitative parameters are expressed as mean ± SEM, and qualitative parameters are shown as *n* (%). Bold indicates variables that demonstrated statistically significant differences between the cohorts. Bold indicates variables that demonstrated statistically significant differences between the cohorts.

abnormal BMI was also similar between the cohorts (26.1 vs. 29.7%, $p = 0.99$). To evaluate dietary behavior, we asked study participants, "How many times per day do you normally eat?" Silent and pain perceptive IBD patients reported statistically similar rates of eating at least three meals each day (62.3% vs. 50.5, $p = 0.13$).

Exercise

To assess recent physical activity, we asked participants, "How many times per week do you exercise?" and "How much time (in minutes) do you spend exercising per week?" The silent and pain perceptive IBD cohorts exhibited similar proportions of individuals exercising at least 3 times per week (55.1 vs. 49.6%, $p = 0.54$). They also reported statistically similar mean numbers of exercise sessions per week (2.8 vs. 2.4, $p = 0.318$) and lengths of time exercising per week (36.2 min vs. 28.6 min, $p = 0.39$) (Table 2).

Sexual Activity

We asked study participants, "In the past month, how many times have you been sexually active?" The silent and pain perceptive IBD cohorts reported similar rates of having sex at least once per month (68.1 vs. 68.4%, $p = 0.99$). They also reported statistically similar mean numbers of episodes of sex over the prior month (3.5 vs. 2.7, $p = 0.34$) (Table 2).

Substance Use

The rates of any tobacco (13.0 vs. 15.3%, $p = 0.83$) and illicit substance use (including cocaine, methamphetamine, and heroin/non-prescription opioid) (5.8 vs. 5.4%, $p = 0.99$) were statistically similar between the cohorts. Alcohol use trended toward being more common in silent IBD patients (40.6 vs. 27.0, $p = 0.07$), while cannabis use was more common in the pain-perceptive IBD cohort (1.4 vs. 10.8%, $p = 0.01$). Prescribed opioid use was similar between the cohorts (4.3 vs. 9.0%, $p = 0.38$). Other pain medication use was more common in the pain-perceptive cohort (24.6 vs. 42.3%, $p = 0.017$) (Table 2).

Multivariable Analysis

In order to evaluate for independent associations with the QP-IBD phenotype, we performed a multivariable logistic regression analysis including the whole quiescent IBD cohort ($n = 180$). We included nine total clinical variables that were found to be significantly directly or inversely associated with the silent IBD

Table 3. Multivariable analysis, associations with silent inflammatory bowel disease

Variable	OR (95% CI)	*p* value
Age	1.01 (0.98–1.03)	0.700
Disease duration	0.99 (0.95–1.03)	0.723
Female sex	**0.35 (0.16–0.74)**	**0.063**
Anxiety/depression symptoms	**0.17 (0.07–0.40)**	**<0.001**
Antidepressant/anxiolytic use	0.72 (0.27–1.91)	0.512
Corticosteroid use	**0.18 (0.04–0.71)**	**0.014**
Opioid use	1.12 (0.19–6.60)	0.899
Cannabis use	0.68 (0.07–7.03)	0.745
EIM ever	0.56 (0.27–1.18)	0.129
Other pain medication use	0.41 (0.15–1.11)	0.080

OR, odds ratio; CI, confidence interval. Bold indicates variables that demonstrated statistically significant differences between the cohorts.

cohort on the bivariate analyses above (female sex, concomitant symptoms of anxiety and/or depression, antidepressant/anxiolytic use, EIMs ever, corticosteroid use, other pain medication use) or had been associated with this cohort on previous analyses (age, disease duration, opioid use). The silent IBD cohort was inversely associated with the female sex, presence of anxiety and/or depression, and corticosteroid use (Table 3).

Discussion

We demonstrated that silent IBD patients are less likely to use cannabis and a variety of pain medications. They also trended toward being more likely to consume alcohol. We found no significant difference in patterns of dietary, exercise, or sexual activity in this study between silent and pain-perceptive IBD patients. As was previously reported, the present study demonstrated that silent IBD is relatively common, in both CD and UC, affecting over one-third of patients with significantly active disease in this investigation. We also found that silent IBD patients were more likely to be male, less likely to have coexistent anxiety and/or depression or EIMs, and less likely to be actively using corticosteroids. Each of these findings was also comparable to what has been reported in other studies attempting to evaluate silent IBD [1–4, 17].

This was the first dedicated study to evaluate the potential influence of lifestyle factors on silent or hypoalgesic IBD. Using a mixture of survey questions, physical examination, and serological data, we found no significant association between dietary, exercise, or sex-related variables and silent IBD. However, we did demonstrate an inverse association between silent IBD and the use of several substances and pharmacological agents frequently used for their perceived analgesic effects (including cannabis, corticosteroids, and antidepressants/anxiolytics) and silent IBD. As previously demonstrated [1], these findings strongly indicate that the silent phenotype is neither being driven by analgesic drug/substance use nor is it apparently being driven by significant differences in IBD type, location, severity, complications, surgical history, or medication regimen (with the lone potential exception of mesalamine) as indicated in the results described above. Instead, the findings of this study support the idea that these individuals simply do not experience personally perceptible and/or impactful levels of abdominal pain, even during phases of significant inflammation (conditions under which other patients are reporting significant abdominal pain).

In spite of the findings outlined above, it is still unclear whether and/or how the lifestyle factors evaluated in this investigation influence the development and course of silent IBD. This study was designed as an initial exploratory evaluation of potential associations between basic elements of lifestyle factors and silent IBD. It was impractical to incorporate all potentially relevant aspects of these variables in this particular study. Nonetheless, there are more specific characteristics of the variables above that warrant further investigation. For example, previous studies have demonstrated that IBD patients who utilize low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diets are less likely to experience abdominal pain [18]. It would be helpful to study whether there is a difference in the proportion of silent and pain-perceptive patients who utilized and/or adhered to this diet. Different physical activities may also affect the likelihood of experiencing abdominal pain in IBD. For example, one prospective study of 100 IBD patients deemed to be in clinical remission on standard medical therapy demonstrated that individuals who participated in at least 1 h of yoga daily over an 8-week span reported a reduced frequency of several symptoms, including "intestinal colic pain" [19]. However, not all forms of exercise may be helpful. This point was illustrated by a survey of IBD patients undertaken in the UK which found that, of the patients that exercised, 72% reported feeling better overall (including 12% who reported improvement in one or more IBD-associated symptoms) as a result of the exercise. However, 23% of respondents reported that exercise made them feel worse, including 17% who described worsening abdominal pain [20]. As above, it would be helpful to evaluate the impact of specific activities in this setting.

This study has other important potential limitations. First, it was undertaken in a single tertiary care center evaluating a predominantly Caucasian population. As this was the case, the findings presented here may not be relevant to every patient group. Second, this is a small study, evaluating relatively small sub-cohorts of CD and UC patients. The more diminutive sizes of these sub-cohorts did not allow for meaningful analyses to evaluate for potential associations between them and the examined lifestyle factors. This fact may have also limited our ability to identify otherwise significant clinical and/or demographic associations. One possible example includes a previously demonstrated differential effect of obesity on clinical outcomes in CD patients but not UC [8]. Third, much of the data were also collected in a retrospective manner, so there was the potential for selection bias, and relevant clinical information may have been missed. Fourth, we were unable to include assessments of other potentially important lifestyle factors, including sleep hygiene and relative stress, both of which have demonstrated potential influence on IBD development and activity [6, 21, 22].

In spite of the issues noted above, this study is important because it highlights several significant and clinically consequential aspects of silent IBD. It is relatively common condition (affecting over one-third of the patients with active IBD evaluated in this study). It is also an impactful condition, being associated with approximately twice the risk of developing intra-abdominal fistulae. Additionally, in spite of the findings described above, it is clear that we still understand very little about the pathophysiology underlying silent IBD. There are clues in the studies undertaken thus far to suggest potential important contributors. Silent IBD is more likely to manifest in males, suggesting a potential role for gonadal hormones in this context. Previous reports indicate that it also more likely to occur in older individuals, raising the possibility that age may affect nociceptive mechanisms (though the present study did not find a significant association in this regard) [1]. We have also recently reported on a genetic marker that is more commonly found in silent IBD patients [3]. However, it is clear based upon the significant numbers of silent IBD patients who do not possess one or more of these characteristics, this is a much more complicated, multifactorial phenomenon. It is important that we gain a more complete understanding of this condition, though, as it will likely lead to important insights regarding how human gastrointestinal pain perception works. It could also help lead to new and potentially safer methodologies for managing chronic visceral pain in IBD and other conditions. This is very important as currently available analgesic options for abdominal management lack of efficacy and/or exhibit significant toxicity, including NSAIDs and opiates [23–26].

In summary, this study demonstrated that silent IBD patients were less likely to use analgesic medications or substances (e.g., cannabis) compared to their pain-perceiving counterparts, in spite of demonstrating similar clinical characteristics. Similar to prior investigations, this study also found that silent IBD patients were independently more likely to be male and less likely to exhibit symptoms of anxiety and/or depression or to use corticosteroids. No other associations were found between silent IBD and the lifestyle factors evaluated here, including those related to dietary, exercise, and sexual variables. However, there are more detailed aspects of each of these variables (including specific diets and physical activities), along with additional lifestyle factors (including sleep hygiene and stress) that need to be examined in future studies.

Acknowledgments

The authors would like to thank Anne Bobb, Thu Thi Gazzio, and Melinda Kuhn (PSHMC IBD Center) along with the staff of the PSHMC Endoscopy Laboratory for assisting with the data collection associated with this study.

Statement of Ethics

This study protocol was reviewed and approved by Penn State College of Medicine Institutional Review Board, approval number STUDY00017310. Written informed consent was obtained from all participants.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research was supported by the Peter and Marshia Carlino Early Career Professorship in Inflammatory Bowel Disease, the Margot E. Walrath Career Development Professorship in Gastroenterology and NIH NIDDK R01 DK122364.

Author Contributions

M.D.C. developed the conceptual framework for this study, prepared the original draft of the manuscript, and assisted in review and editing of the manuscript. S.D. assisted with review and editing of the manuscript. A.S. assisted with data collection and organization and assisted with review and editing of the

manuscript. V.W. assisted with data analysis and review and editing of the manuscript. A.T., K.C., and E.D.W. assisted with data collection and manuscript review and editing. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated during this study are included in the article. Further inquiries can be directed to the corresponding author.

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