

Inflammatory bowel disease and addiction: more than just smoke?

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Abstract

Background Inflammatory bowel disease (IBD) is associated with comorbidities, including psychiatric disorders. However, evidence on concomitant addictions among IBD patients is lacking.

Methods This prospective multicenter cross-sectional analysis investigated the prevalence of the most common addictions (alcohol, nicotine, drugs, food and gambling) in patients with IBD in Germany, with a focus on differences between Crohn's disease (CD) and ulcerative colitis (UC). Adult patients completed questionnaires covering addictive behavior, IBD-related and general information. Data were analyzed using standard statistical tests and correlation analyses (significance level $P < 0.05$).

Results The study was conducted from April to October 2018, and 202 patients were included in the analysis (67.3% CD; 32.7% UC). Overall addictive behavior and nicotine addiction were more frequent in CD than in UC patients (overall: 41.2% vs. 24.3%; nicotine: 23.5% vs. 9.1%). Alcohol addiction was found in 4.9% of patients, with similar rates in CD and UC. Nicotine addiction was more frequent among females, alcohol addiction among males. Drug, food and gambling addictions were less common (5.0%, 2.0% and 0.5%) and presented only in CD patients. Significant associations were found between addictive behaviors and small intestine involvement, between nicotine addiction and educational qualification, as well as between alcohol addiction and cardiovascular risk factors, comorbidities and body mass index.

Conclusions Over a third of IBD patients exhibit addictive behaviors, with smoking being most prevalent, especially among CD patients. These findings support the recent literature, and highlight the need for interventions to address addiction risks and improve outcomes in CD and UC.

Keywords Inflammatory bowel disease, addictive behavior, Crohn's disease, ulcerative colitis, comorbidities

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Introduction

Inflammatory bowel disease (IBD) has become a global disease, with its burden remaining high in western countries and its incidence rising in newly industrialized countries. Recent data report highest prevalence rates for IBD in Europe and North America [1]. IBD covers a broad spectrum of chronic inflammatory conditions with systemic effects and potentially complex and debilitating disease courses.

Several comorbidities are associated with IBD, influencing not only the burden of the disease, but also the efficacy of existing therapies. A growing body of data dealing with comorbidities and extraintestinal manifestations has resulted in specific recommendations for patient management [2]. In this context, the connection between IBD and psychiatric comorbidities is well known; these include depression, anxiety disorder, bipolar disorder and schizophrenia [3]. Existing data also suggest a higher prevalence of substance use, particularly opioid use, alcohol abuse and other addictions in patients with IBD [4-6].

However, knowledge is lacking about the simultaneous presence of the most common addictions in IBD patients,

taking into account the analysis of potential confounding factors such as depression and disease activity. Furthermore, there are no structured data that simultaneously analyze several other common addictions, such as recreational drug abuse, food addiction and gambling addiction, in patients with IBD. Therefore, the influence of substance abuse, in combination with further addictive behavior, on patients' treatment compliance, the effectiveness of anti-inflammatory drugs and consequently the course of the disease, remains understudied.

The aim of this study was to investigate the concomitant prevalence of the most common addictions in patients with IBD, and to identify differences in addictive behavior between patients with Crohn's disease (CD) and those with ulcerative colitis (UC). We hypothesized that complex psychosocial and medical factors could result in a higher prevalence of common addictions. Our results should support the targeted development of evidence-based recommendations for gastroenterologists and general practitioners, helping to optimize the diagnosis and treatment of IBD patients.

Patients and methods

Study design

This prospective, multicenter, cross-sectional analysis was conducted in the period from April to October 2018 at 6 specialized IBD inpatient and outpatient departments of university and regional hospitals, as well as at private practices in Germany. A large proportion of the patients were recruited in the IBD outpatient department of the University Hospital of Erlangen. The primary objective was to investigate the prevalence of the most common addictions in patients with IBD, by asking them to fill out a questionnaire, and to identify differences in addictive behavior between CD and UC.

The 6 most common addictions in Germany were evaluated, i.e., alcohol, nicotine, legal and illegal drug addictions, eating disorders (e.g., food addiction or anorexia), and gambling addiction [7]. This study refrained from investigation of further addictions, given their modest prevalence, in order to maintain the participants' compliance, even though this limited the statistical power of the analysis.

Patients

All patients had to be at least 18 years of age and had to have an established diagnosis of IBD according to the German (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, DGVS) [8,9] and European guidelines (European Crohn's and Colitis Organisation) [10,11], based on characteristic clinical signs and symptoms, laboratory, endoscopic and histological findings, as

well as typical imaging (particularly using ultrasonography and magnetic resonance imaging).

Patients were identified and asked by the treating study doctors to participate in this study. Patients with insufficient language skills to complete the questionnaire in the German language were excluded from this study. In the present analysis, no imputation was performed. For each parameter, analyses were conducted using all available (non-missing) observations.

Assessments

The study used a paper-based patient-reported anonymous questionnaire with 87 questions covering validated and internationally established screening tests for addictive behavior, IBD-related information, general health status, and socioeconomic, as well as demographic data. The screening tools used to evaluate addictive behaviors in the questionnaire are briefly summarized in Supplementary Table 1. The following cutoff thresholds were used to identify addictive behaviors: daily smoking for nicotine use; ≥ 2 positive responses in the CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire for problematic alcohol use; the presence of ≥ 3 symptoms plus clinically significant impairment or distress in the modified Yale Food Addiction Scale (mYFAS) questionnaire for food addiction; ≥ 7 positive responses in the Gamblers Anonymous 20 Questions (GA20) screening test for compulsive gambling; and ≥ 3 points in the Drug Abuse Screening Test (DAST-10). Validation studies of the German versions of these instruments have been published (Supplementary Table 1). Regarding our novel and tailored study approach of simultaneously evaluating several addictions in IBD patients, there is no explicit validation available regarding the overall battery of the abovementioned tests, nor was a pilot-test conducted. However, data have been published on the use of this same composite tool in a dermatological setting [12].

Assessment of IBD-related information included diagnosis, disease course, disease duration, initial manifestation, current treatment (e.g., glucocorticoid treatment), intestinal sections affected, extraintestinal manifestations, and clinical disease activity measured by the PRO-3-Score. The PRO-3-Score contains questions about the number of liquid stools, abdominal pain and general well-being in the last 7 days. Questions on general health status included family history and comorbidities (arterial hypertension, thromboembolic events, metabolic diseases, lung diseases, allergic diathesis, mental illnesses). Socioeconomic data included information on educational degree and profession. Demographic data contained sex, age, height and weight. Body mass index (BMI) was calculated from body height and weight.

Administrative procedures

Approval for this study was obtained by the local ethics committee of the medical faculty of the Friedrich-Alexander-

University Erlangen-Nürnberg. All patients provided written informed consent before participating in this study.

Data managements and statistical analysis

The data received from the questionnaires were transferred into a database using Microsoft Office Excel 2006 (Redmond, USA). Statistical analyses were performed using IBM SPSS Statistics, versions 24 and 26 (Armonk, USA), as well as R 3.6.3 (Vienna, Austria). Categorical variables are presented as number and proportion of patients. Continuous variables are shown as mean together with standard deviation (SD), or median with range. Statistical analyses included *t*-tests, Chi² tests, Fisher's exact tests, Mann-Whitney *U* tests, and Pearson's correlations. The level of significance was set at 5% ($P=0.05$).

Results

Analysis population

In total, 229 patients agreed to participate and answered the questionnaire. Of these, 27 patients were excluded from analysis because of missing information regarding diagnosis or sex, or a diagnosis of indeterminate colitis. Finally, 202 patients were included in the analysis population, 67.3% with a CD diagnosis and 32.7% with UC (Table 1). Supplementary Fig. 1 depicts the participant flow according to the STROBE guidelines.

Non-completion rates were 1.5% ($n=3$) for the questionnaire on smoking behavior, 11.4% ($n=23$) for the CAGE questionnaire on alcohol addiction, 23.8% ($n=48$) for the mYFAS on food addiction, 25.2% ($n=51$) for the GA20 on gambling addiction, and 20.3% ($n=41$) for the DAST-10 on drug addiction.

Demographic and disease characteristics

Overall, the sex distribution was almost equally balanced, with 46.5% male and 53.5% female study participants. Analysis of sex distribution by disease showed a larger proportion of female than male patients with CD (40.6% vs. 26.7%), and a larger proportion of male than female patients with UC (19.8% vs. 12.8%) (Table 1). The mean age of all patients diagnosed with CD was 38 years, compared to a mean age of 40 years in the group of patients with UC (Table 1).

Among CD patients, 34.6% had a higher education entrance qualification, or already held a university or a college degree (i.e. at least completed secondary education level). Similarly, in the group of patients diagnosed with UC, 39.3% met the criteria to apply for university or college or had already graduated (Table 1).

Depression was reported by 4% of patients with CD and 2% of patients with UC, while 8.4% of patients with CD and

5.9% of patients with UD reported currently receiving oral glucocorticoids (Table 1). Additional patient characteristics are displayed in Table 1.

Overall addictive behavior

Altogether, 72 patients (35.6%) of the overall population were identified as showing addictive behavior. In the CD population, 56 (41.2%) patients were affected, compared to 16 (24.2%) patients in the UC population (Fig. 1); this difference was statistically significant (Tables 2 and 3).

Statistically significant associations with overall addictive behavior were also found for small intestine involvement. Among patients with small intestine involvement and complete information on addictive behavior ($n=77$), 24.8% ($n=28$) had no addictions, compared to 43.4% ($n=49$) who showed addictive behavior (Table 2). Among the subgroup of CD patients, a significant association was identified between the categorical PRO score as a parameter for clinical disease activity and the presence of overall addictive behavior ($P=0.021$; Fisher's exact test). The direction of this association could not be determined based on the available data.

Nicotine addiction

In the analysis population, 18.8% of patients were daily smokers and were thus classified as addicted to nicotine (Fig. 1). Analysis by diagnosis revealed nicotine addiction in 23.5% ($n=32$) of patients with CD and 9.1% ($n=6$) of patients with UC (Fig. 1); this difference was statistically significant (Tables 2 and 3).

An analysis by sex revealed that 25.9% ($n=28$) of all female IBD patients presented a nicotine addiction, compared to 10.6% ($n=10$) of all male IBD patients. This difference was statistically significant (Tables 2 and 3).

A statistically significant inverse association with nicotine addiction was also found for educational qualification. Accordingly, 25.0% ($n=32$) of patients with lower educational qualifications were daily smokers, compared to 8.2% ($n=6$) of patients with higher educational qualifications (Tables 2 and 3).

Alcohol addiction

The presence of alcohol addiction according to the CAGE questionnaire (>2 points) was identified in 4.9% of patients in the overall IBD population (Fig. 1). Analysis by diagnosis revealed alcohol addiction in 4.4% ($n=6$) of CD patients and in 6.1% ($n=4$) of UC patients (Fig. 1). This difference was not statistically significant (Table 2).

Analysis by sex identified alcohol addiction in 1.9% ($n=2$) of all female IBD patients and in 8.5% ($n=8$) of all male IBD patients. This difference was statistically significant (Tables 2 and 3).

Table 1 Patient characteristics

Characteristics	CD (n=136)	UC (n=66)	Total (n=202)
Sex, n (%)			
Male	54 (39.7)	40 (60.6)	94 (46.5)
Female	82 (60.3)	26 (39.4)	108 (53.5)
Age in years			
Mean (SD)	38.0 (14.07)	39.7 (15.45)	38.5 (14.49)
Median (range)	35.0 (19.0-77.0)	36.0 (20.0-78.0)	35.0 (19.0-78.0)
Educational qualification, n (%)			
Secondary education II ^a	47 (34.6)	26 (39.4)	73 (36.1)
Secondary education I ^b	88 (64.7)	40 (60.6)	128 (63.4)
BMI in kg/m ² , mean (SD)			
Mean (SD)	25.0 (5.26)	24.6 (4.49)	24.5 (5.01)
Median (range)	23.7 (15.6-52.5)	24.0 (17.1-37.1)	23.8 (15.6-52.5)
No. of cardiovascular risk factors			
Mean (SD)	2.5 (1.01)	2.6 (1.13)	2.5 (1.05)
Median (range)	2.0 (1.0-7.0)	2.0 (1.0-7.0)	2.0 (1.0-7.0)
Course of disease, n (%)			
1-Time flare	16 (11.8)	9 (13.6)	25 (12.4)
Mild disease	10 (7.4)	3 (4.5)	13 (6.4)
Recurrent flares	70 (51.5)	33 (50.0)	103 (51)
Chronically active	35 (25.7)	20 (30.3)	55 (27.2)
Not specified	5 (3.7)	1 (1.5)	6 (3.0)
Positive family history regarding IBD, n (%)	11 (8.1)	5 (7.6)	16 (7.9)
Age at initial diagnosis in years			
Mean (SD)	24.4 (10.65)	28.9 (13.25)	25.9 (11.74)
Median (range)	21.0 (5.0-63.0)	27.0 (2.0-64.0)	23.0 (2.0-64.0)
Duration of IBD in years			
Mean (SD)	14.0 (10.9)	11.4 (11.0)	13.2 (11.0)
Median (range)	11.0 (1.0-50.0)	7.0 (1.0-52.0)	10.0 (1.0-52.0)
Upper GI-involvement, n (%)	41 (30.1)	0 (0)	41 (20.3)
Small intestine involvement, n (%)	110 (80.9)	3 (4.5)	113 (55.9)
Large intestine involvement, n (%)	67 (49.3)	59 (89.4)	126 (62.4)
Clinical remission according to PRO3-score, n (%)	63 (46.3)	27 (40.9)	90 (44.6)
Presence of extraintestinal manifestations, n (%)	73 (53.7)	30 (45.5)	103 (50.9)
Presence of comorbidities ^d , n (%)	23 (16.9)	13 (19.7)	36 (17.8)
No. of comorbidities ^d			
Mean (SD)	0.7 (1.09)	0.8 (1.39)	0.7 (1.21)
Median (range)	0 (0-4)	0 (0-5)	0 (0-5)
Presence of depression, n (%)	8 (5.9)	4 (6.1)	12 (5.9)
Current glucocorticoid treatment, n (%)	17 (12.5)	12 (18.2)	29 (14.4)

^acomparable to senior high school diploma, college/university degree; ^bcomparable to junior high school or no degree; ^carterial hypertension, thrombosis, myocardial infarction, apoplexy, diabetes mellitus, dyslipidemia, obesity; ^dhypertension, thrombosis, myocardial infarction, apoplexy, diabetes mellitus, hypercholesterolemia, bronchial asthma, chronic obstructive pulmonary disease, sleep apnea, pollinosis, recurrent tonsillitis, thyropathy, depression
 BMI, body mass index; CD, Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; PRO, patient-reported outcome; SD, standard deviation; UC, ulcerative colitis

Statistically significant associations with alcohol addiction were also found for the number of cardiovascular risk factors, the number of comorbidities, and BMI (Table 2). Accordingly, patients with alcohol addiction had more cardiovascular risk factors (Fig. 2) and more comorbidities (Fig. 3). The CAGE score and the BMI value correlated moderately positively ($r=0.208$; $P=0.005$).

Further addictions

Drug addiction was identified in 5.0%, food addiction in 2.0%, and gambling addiction in 0.5% of patients in the overall population (Fig. 1). All drug-, food- and gambling-addicted patients had been diagnosed with CD. No statistically significant associations between drug addiction and patient characteristics

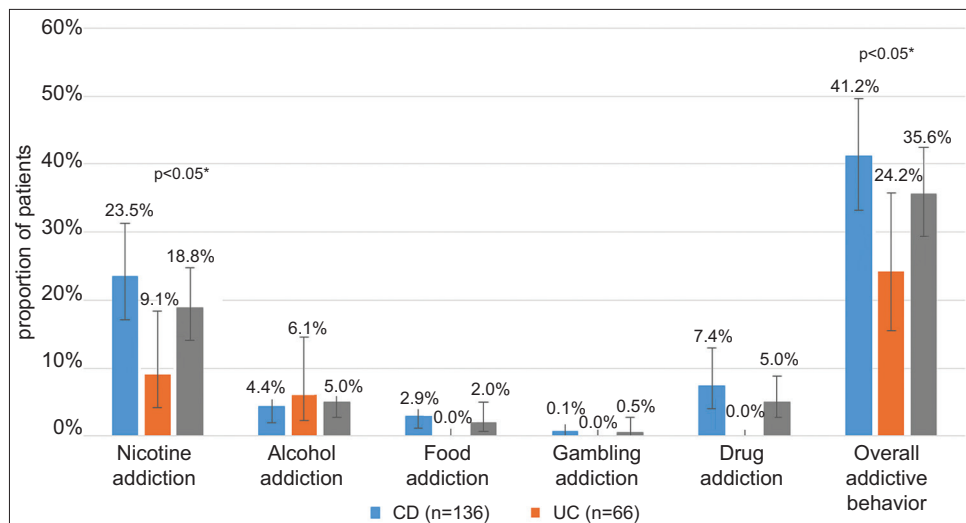


Figure 1 Proportions of patients with addictive behavior by type of addiction and overall addictive behavior in the overall population, as well as in the subpopulations of patients with CD and UC. Definitions: nicotine addiction defined as daily smoker; alcohol addiction defined as CAGE ≥ 2 points; food addiction defined as at least 3 of the questions on dependent behavior answered positively, in combination with the indication of at least 1 clinically significant restriction; gambling addiction defined as ≥ 7 questions in GA20 answered with “yes”; drug addiction defined as ≥ 3 questions in DAST10 answered with “yes”

*for comparison between CD and UC. Error bars indicate 95% confidence interval
CD, Crohn's disease; UC, ulcerative colitis

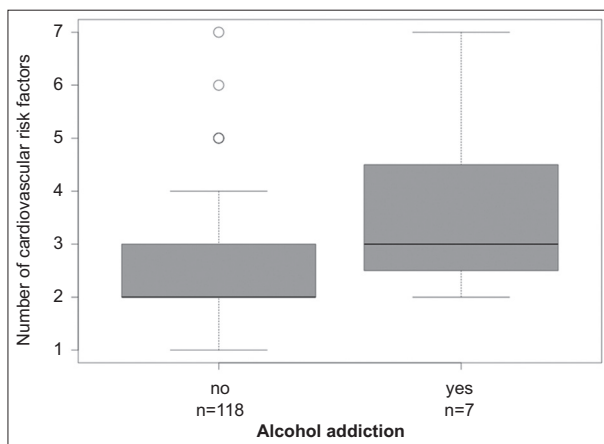


Figure 2 Boxplot of association between alcohol addiction and number of cardiovascular risk factors. Boxes represent the interquartile range (IQR) with the median indicated; whiskers extend to $1.5 \times \text{IQR}$, and outliers are shown as individual points

were identified. Statistical analyses of food and gambling addiction were not performed given the small number of cases.

Discussion

The guidelines of the European Crohn's and Colitis Organisation (ECCO) recommend treating comorbidities in IBD patients, including psychiatric disorders, given their significant impact on disease course [10,11]. Psychiatric comorbidities are associated with greater mortality in

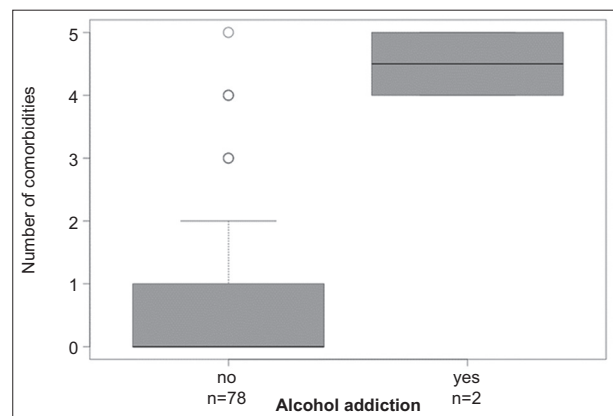


Figure 3 Boxplot of association between alcohol addiction and number of comorbidities. Boxes represent the interquartile range (IQR) with the median indicated; whiskers extend to $1.5 \times \text{IQR}$, and outliers are shown as individual points

immune-mediated inflammatory diseases [13] and surgery risk in CD [14]. Recognition of addictive behavior in CD or UC patients is crucial for adequate treatment.

In this study, addictive behavior was identified in over one third of CD and UC patients. Smoking addiction was most prevalent, affecting one fifth of patients, while alcohol and drug addiction each affected 5%. Food and gambling addictions were less common. CD and UC patients showed different addiction risks. While alcohol addiction rates were similar between groups, smoking addiction was more prevalent in CD patients, and drug addiction was recorded only in CD patients.

The literature shows a varying prevalence of nicotine addiction among IBD patients, with higher smoking rates

Table 2 Statistically significant differences in addictive behavior by demographic and disease variables

Variable	Test	Nicotine addiction	Alcohol addiction	Drug addiction	Overall addictive behavior ^a
		P-value	P-value	P-value	P-value
Diagnosis	Fisher's exact test	0.014	0.734	n.a.	0.007 (Chi ²)
Sex	Fisher's exact test	0.008	0.046	n.a.	n.a.
Age	t-test	0.861	0.816	n.a.	n.a.
Educational qualification	Fisher's exact test	0.016	0.990	n.a.	0.053 (Chi ²)
BMI	Mann-Whitney U test	0.582	0.024	0.091	0.496
Cardiovascular risk factors	Mann-Whitney U test	0.696	0.028	n.a.	0.172
Disease course	Fisher's exact test	0.592	0.404	0.471	0.293
Family history	Fisher's exact test	0.250	>0.99	>0.99	0.172
Age at initial diagnosis	Mann-Whitney U test	0.480	0.213	0.104	0.631
Duration of IBD	Mann-Whitney U test	0.674	0.837	0.111	0.645
Upper GI-involvement	Fisher's exact test	0.703	0.686	>0.99	0.832
Small intestine involvement	Fisher's exact test	0.056	>0.99	>0.99	0.019
Large intestine involvement	Fisher's exact test	0.505	0.486	>0.99	0.072
PRO3 (categorical) ^b	Fisher's exact test	0.349	0.599	0.237	0.166
Extraintestinal symptoms	Mann-Whitney U test	0.951	0.482	0.306	0.801
Comorbidities	Mann-Whitney U test	0.598	0.009	n.a.	0.122
Depression	Fisher's exact test	0.341	>0.99	n.a.	0.322
Glucocorticoid use	Fisher's exact test	0.514	0.642	>0.99	0.787

P-values <0.05 indicate statistically significant differences in the prevalence of addictive behavior.

^aincludes nicotine, alcohol, drug, food, and gambling addiction; ^bclinical remission yes/no

BMI, body mass index; GI, gastrointestinal; IBD, inflammatory bowel disease; PRO, patient-reported outcome

in CD than in UC patients [15-17]. It has been reported that CD patients who smoke face a higher risk of severe disease progression [2,9,10], regardless of the amount of nicotine consumed [18]. Since our cross-sectional study design only allows the identification of associations, the study could not determine whether smoking triggered CD onset, or if the disease burden led to nicotine dependence. It is noteworthy that, in UC, nicotine has been reported to be protective against disease activity [8], with disease onset or exacerbation after smoking cessation [15].

Compared to publicly available German general population data, the present results suggest that CD patients have a higher nicotine addiction risk. A survey of 20 million persons showed that 15.1% of the general population consume cigarettes daily [19], compared to 23.5% of our CD population. Unlike the German general population [19], more women than men were addicted to nicotine in our CD subpopulation—this could possibly be explained by the female predominance. The association of low-level education with increased nicotine addiction risk in IBD patients aligns with general German

population observations [20]. In contrast to our findings, literature reports indicate similar smoking prevalence between IBD patients and the general population, though they lack detailed subgroup analyses comparing CD and UC [16]. However, current data suggest a high smoking relapse risk in CD patients [21], which should be considered when establishing cessation support measures.

There are only limited data on the prevalence of new smoking devices in IBD patients and their disease impact. Cross-sectional and case-control studies found a 5-10% rate of e-cigarette use in IBD patients, with no clear indication of worse outcomes [16,22]. Further research is needed to determine the effects of e-cigarettes on IBD outcomes.

The statistically significant association between alcohol addiction and sex in IBD patients, with a higher prevalence in males than females, aligns with general German population trends [23]. Alcohol addiction affected 8.5% of male IBD patients in our study, versus 1.9% of female IBD patients. Alcohol use increases the risk of relapse and has harmful effects [24], including altering the gut microbiome, disrupting

Table 3 Effect sizes (OR with 95% CI) for key associations

Variable	Addiction	Group 1 nc/n	Group 2 nc/n	OR 95%CI	P-value
Diagnosis	Nicotine addiction	MC 32/134	UV 6/65	3.0769 [1.2164, 7.7833]	0.014
Diagnosis	Overall addictive behavior ^a	MC 56/88	UC 16/43	2.9351 [1.3871, 6.2873]	0.007 (chi ²)
Sex	Nicotine addiction	Male 10/91	Female 28/108	0.3527 [0.1608; 0.7736]	0.008
Sex	Alcohol addiction	Male 8/83	Female 2/96	5.0133 [1.0337; 24.314]	0.046
Educational qualification	Nicotine addiction	Secondary Level I 32/127	Secondary Level II 6/71	3.6491 [1.4437; 9.2237]	0.016

^aincludes nicotine, alcohol, drug, food, and gambling addiction

nc: Number of patients with characteristic, n: total number of patients in the specific group

CD, Crohn's disease; CI, confidence interval; OR, odds ratio; UC, ulcerative colitis

the intestinal barrier, and increasing intestinal inflammation and permeability. Furthermore, alcohol can interact with medications, such as antibiotics, 5-aminosalicylates, cyclosporine, thiopurines, methotrexate and potentially anti-tumor necrosis factor antibodies [24], leading to worse side-effects [25]. Recent findings from a Swiss IBD cohort show that heavy alcohol consumption is most common in male smokers aged >50 years [26]. Given that alcohol use is even more frequent than previously reported in the US population [5], regular screening and support for IBD patients is necessary to limit problematic consumption.

In our study, small bowel infestation was associated with overall addictive behavior, though case numbers were too limited for analysis by disease location. Disease activity measured by PRO score showed significant association with addictive behavior, particularly in CD patients. The direction of this association is unclear, with both negative and positive correlations possible. According to the literature, addictive behavior may serve as a coping strategy, increasing with disease activity [27]. This is especially relevant for opioid analgesics, which can relieve pain and diarrhea in active IBD [9]. Recent data show that opioid use, especially stronger formulations, correlates with a higher risk of intestinal resection and psychological comorbidity [28].

IBD activity decreases quality of life through frequent bowel movements, malnutrition and pain. Abstaining from large meals and selecting well-tolerated foods promote symptom relief [29]. Recent data highlight connections between dietary behavior and disease activity in IBD patients [30,31]. This may explain why primary food addiction was found in only 2.0% of patients, limiting detailed analyses of food addiction. The current literature on eating disorders in IBD focuses on, e.g. anorexia nervosa and food avoidance, but no reports have

indicated higher food addiction rates in IBD patients compared to the general population [32,33]. However, growing awareness of the influence of nutrition on IBD [34] may even promote opposite reactions, with recently published data suggesting an increased risk of orthorexia in IBD patients [35].

Since only 0.5% of our study population had a gambling addiction, statistical subgroup analysis was not feasible, as the limited statistical power precluded further exploration of gambling behavior in IBD. However, gambling addiction may be underestimated, as published data show problematic gambling in 1.41% of adults [36]. Given the relationships between gambling disorder, substance use, mood and anxiety disorders [37], and increased psychiatric comorbidity in IBD patients, the risk of gambling addiction in IBD patients might be higher, as our data suggest. Future research should examine gambling addiction, including online gaming, in IBD patients, with a focus on the effects of COVID-19 restrictions and limited working capacity.

In our study, comorbidities were unsurprisingly associated with alcohol dependence, as alcohol consumption promotes chronic illnesses [38,39]. However, in our analysis of confounding factors we found no significant association between depression and nicotine, alcohol or drug addiction, despite their known complex relationship [40]. Furthermore, it has to be noted that there are links between IBD and neuropsychiatric disorders, including depression and anxiety disorders based on alterations in the microbiome-gut-brain-axis [41,42]. This could possibly explain the higher prevalence of addictive behavior in IBD patients, although the small sample sizes meant that we could not identify an association between depression and addiction in our study. Similarly, while glucocorticoids increase drug abuse vulnerability [43], we found no significant association between glucocorticoid

use and addictions. In contrast, our study revealed that alcohol addiction is positively related to BMI, with a higher BMI associated with higher CAGE scores, possibly because of the high glycemic index of ethanol [44]. Discrepancies between our study results and expected outcomes as per published literature data warrant further investigation beyond the scope of the present study. Differences in measurement approaches, sample size, and potential underreporting may have contributed to these discrepancies; a more comprehensive evaluation in a systematic literature analysis would be required to investigate these aspects in depth.

Our study was not designed to identify further demographic risk factors for addictive behavior. However, the literature shows that young age, low education, non-white ethnicity and occupational status are linked to alcohol or drug dependence, unlike sex, number of children or residential area [45]. Addictive behavior is influenced by factors that include a family history of substance abuse, psychiatric disorders and trauma disorders [46,47].

This study was the first to simultaneously examine 6 common addictions in IBD patients in a German population. However, limitations should be considered. First, the questionnaire required on average 14 minutes to complete, which patients found too long. This resulted in incomplete data, particularly affecting the GA-20 and the DAST-10 tools placed later in the form. This probably reflects respondent fatigue, rather than systematic bias, suggesting the missingness was largely random. Missing data increased uncertainty in subgroup analyses, where statistical power was already limited by small sample sizes, and prevented further statistical testing in subgroups.

Second, patient recruitment in IBD outpatient clinics led to an uneven distribution, with CD patients being twice as numerous as UC patients. Non-representative sampling of patients from tertiary centers also leads to a possible selection bias. Additionally, the study lacked controls to compare results with the general population in Germany, since the multicenter design, including a large tertiary referral center as well as private practices, did not allow standardized recruitment of controls. Despite efforts, raw data from the German DEBRA study were not accessible to perform a comparative analysis of nicotine addiction.

Furthermore, the original versions of the screening instruments are non-German, and validation data for Germany and its heterogenic regions is limited, restricting cross-cultural comparability. Another limitation was missing data on ethnic discrimination in the questionnaire, as addictive behavior varies across ethnic groups [48]. However, most patients had Caucasian backgrounds, precluding ethnic-based subgroup analysis.

The cross-sectional design prevented distinct testing of the observed associations, and no structured database exists for a longitudinal analysis of addictions in IBD patients. No formal adjustment for multiple testing was applied, as the study was designed to be exploratory rather than confirmatory. The reported P-values are therefore considered descriptive. The results are hypothesis-generating and need confirmative evaluation. Future research should address regional variation

in addictive behavior using international multicenter settings, as our data only apply to the German population.

In conclusion, addressing addictive behaviors in IBD patients is crucial for disease management. Over one third of IBD patients show addictive behaviors, predominantly smoking among CD patients. These findings call for the integration of addiction screening in IBD care pathways, in line with ECCO and DGVS guidance, as well as for targeted interventions in CD and UC patients to improve outcomes and quality of life [49,50].

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Summary Box

What is already known:

- Inflammatory bowel disease (IBD) is associated with a high burden of comorbidities, including psychiatric disorders
- Addictive behaviors, such as smoking and alcohol use, are known to influence disease course and outcomes in IBD
- Previous studies have mainly focused on single addictive behaviors rather than their co-occurrence

What the new findings are:

- More than one third of IBD patients exhibit at least 1 addictive behavior, with higher rates in Crohn's disease than in ulcerative colitis
- Nicotine addiction is the most prevalent form of addiction, particularly among patients with Crohn's disease and among females
- Other addictive behaviors (drug, food and gambling) are rare, and are predominantly observed in Crohn's disease, highlighting the need for further research

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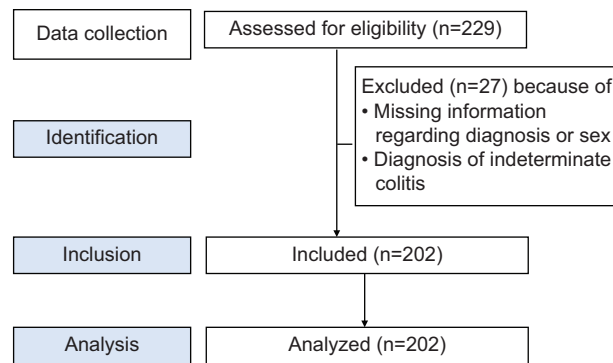
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Supplementary material

Supplementary Table 1 Summary of screening tools used in the questionnaire to evaluate addictive behaviors

Tobacco / Smoking behavior	<i>Pack years and cumulative pack years</i> • Frequency of smoking - Non-smokers - Irregular/seldom-smokers - Regular/daily-smokers • Number of cigarettes smoked every day (semiquantitative): - less than 1 pack per day - 1 pack per day - 1.5 packs per day - 2 packs per day - More than 2 packs per day • Total years of smoking
Alcohol abuse	<i>Cumulative amount of alcohol consumed by each individual</i> • Frequency: - Never - Once per month or less often - 2-4 times per month - 2-3 times per week - More than 4 times per week • Quantity of alcoholic beverages consumed each time (considering 1 'glass' to be equivalent to 1 bottle of beer or cider, ¼ bottle of wine or sparkling wine, or 1 measure of hard liquor [2 cL]): - 1-2 glasses - 3-4 glasses - 5-6 glasses - 7-9 glasses - 10 or more glasses
	<i>CAGE questionnaire</i> • Internationally well-established and extensively validated screening test to evaluate alcohol problems and alcoholism. • Contains 4 specific questions, forming the acronym 'CAGE': [1] - Have you ever felt you should Cut down on your drinking? - Have people Annoyed you by criticizing your drinking? - Have you ever felt bad or Guilty about your drinking? - Eye opener: have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover? • An existing risk of alcoholism is assumed if 2 or more questions are positively answered, leading to a recommendation for further investigation. A score of 4 is virtually diagnostic for alcoholism [2]. Existing validity studies of the CAGE questionnaire calculate a sensitivity of up to 91% and a specificity of up to 97% for ≥2 answers marked with 'yes' to identify problematic drinking behavior [3].
Food addiction	<i>The modified Yale Food Addiction Scale (mYFAS)</i> • This represents a shortened version of the Yale Food Addiction Scale, which was developed to perform an assessment for addictive-like eating behavior using 25 items [4]. • Despite remaining differences among researchers about the precise definition of "food addiction", the YFAS represents the first standardized assessment tool to identify persons with food dependency based on the 7 substance-dependence criteria in the DSM-IV. It does not depend on body weight, and evaluates 7 food addiction symptoms in combination with signs of clinically significant impairment and distress. • The mYFAS contains only 9 questionnaire items, and targets the screening of large epidemiologic cohorts. It was validated in 2014, with its prevalence rates of food addiction diagnoses and its validity indices shown to be comparable to those obtained using the full version [5]. Herein, 1 item for each of the 7 symptoms of substance dependence in the DSM-IV is used, and 2 items assess the existence of a clinically significant impairment or distress. • The presence of at least 3 symptoms and the criterion of a clinically significant impairment or distress result in the diagnose of "food addiction". Participants meeting the threshold criteria only partially are assigned to the category "risk of food addiction".
Gambling	<i>Gamblers Anonymous Twenty Questions (GA-20)</i> • This tool is provided as a self-developed screening instrument by the worldwide organization Gamblers Anonymous [6]. This fellowship was founded in 1957 by obsessed gamblers to prevent a relapse of their gambling addiction. • The GA-20 was developed based on their personal experiences to help other compulsive gamblers. It has been thoroughly validated and is used worldwide as a self-assessed measurement to detect gambling problems [6]. • A compulsive gambling behavior can be assumed if ≥7 questions are answered with 'yes'.
German versions	Validation studies of the German versions of the instruments have been published [7–11].

DSM-IV, diagnostic and statistical manual of mental disorders; GA-20, Gamblers Anonymous twenty questions; mYFAS, modified Yale food addiction scale



Supplementary Figure 1 Participant flow diagram according to STROBE guidelines

Data and material included in this research article can be accessed by contacting the corresponding author

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