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# **Complete Endoscopic Healing is Associated with Lower Disability than Partial Endoscopic Healing in Crohn's Disease: a Prospective Multicenter Study**

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**Short Title:** Disability and Mucosal Healing in Crohn's Disease

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Study concept and design: CY, MF

Acquisition of data: CY, BD

Analysis and interpretation of data: CY, FB, MD, MF

Drafting of the manuscript: CY, MF

Critical revision of the manuscript for important intellectual content: CY, FB, MD, MF

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**Study Highlights:**

## WHAT IS KNOWN

- Disability in Crohn's disease (CD) patients is common.
- Endoscopic healing is now recognized as one of the main therapeutic targets by international guidelines
- The level of endoscopic healing needed to achieve lower disability is unknown

## WHAT IS NEW HERE

- One-third of CD patients in endoscopic remission as defined by a CDEIS <4 experienced moderate to severe disability.
- Complete endoscopic healing (CDEIS = 0) is associated with significantly lower disability than partial endoscopic healing (CDEIS >0 and <4).
- Patients with complete endoscopic healing had lower median defecation and energy IBD-Disk sub score.
- Deeper endoscopic healing may be needed to reduce the risk of disability in CD.

## Abstract

**Introduction:** Crohn's disease (CD) has a significant impact on health status and quality of life, affecting physical and emotional well-being and impairing social and functional abilities. In the era of the treat-to-target concept, endoscopic healing has emerged as the goal to achieve to prevent intestinal damage and disability. It is not clear what level of endoscopic healing is associated with lower disability. We therefore aimed to compare disability associated with complete endoscopic healing to disability with partial endoscopic healing in patients with CD.

**Methods:** We conducted a multicenter prospective study, between September 2019 and November 2020, in one university hospital, one general hospital, and one private practice center. Consecutive patients with CD in clinical remission were included, having either **complete endoscopic healing (CDEIS = 0)** or **partial endoscopic healing (CDEIS >0 and <4)**. **The 10-item IBD-Disk self-assessment questionnaire was used to assess disability.** Moderate to severe disability was defined as an overall IBD-Disk score  $\geq 40$ .

**Results:** A total of 82 patients were included. Forty-four (53%) were women, the median age and disease duration were respectively 35.3 years (interquartile range [IQR], 28.6-45.2) and 8.0 years (IQR, 3.0-17.0). The median overall IBD-Disk score was 26.5 (IQR, 9 -45.0), and 30 (36.6%) patients had moderate to severe disability. Complete endoscopic healing was observed in 48 patients (57.3%). The median IBD-Disk score was respectively 24 (IQR, 9.0-40.5) and 34 (IQR, 9.5-51.5) for patients with complete and partial endoscopic healing ( $p=0.068$ ). Respectively, 13/48 (27%) and 17/34 (50%) of patients with complete and partial endoscopic healing had moderate to severe disability ( $p=0.039$ ). In multivariate analysis, partial endoscopic healing (OR=5.82, 95% CI [1.65, 24.69],  $p=0.0009$ ), female gender (OR=4.0, 95%CI [1.13, 16.58],  $p=0.04$ ), and smoking (OR=8.33, 95% CI [1.96, 50.0]  $p=0.006$ ) were significantly associated with moderate to severe disability. Among the IBD-Disk sub scores, the defecation score (median, IQR) (0.0 [0.0-3.0] vs 4.0 [0.0-7.5],  $p=0.028$ ) and energy score (4.0 [0.0-6.0] vs 6.0 [2.5-8.0],  $p=0.023$ ) were significantly lower with complete endoscopic healing.

**Conclusions:** One-third of patient with endoscopic healing reported moderate to severe disability. Complete endoscopic healing (CDEIS = 0) was associated with lower disability than partial endoscopic healing (CDEIS >0 and <4). Deeper endoscopic healing may be needed to reduce the risk of disability in CD.

## Introduction

Crohn's disease (CD) has a significant impact on patients' health status and quality of life, affecting physical and emotional well-being and impairing social and functional abilities (1). Therefore, new standards of care, taking into account IBD-related disability and daily-life burden are becoming increasingly widespread in clinical practice.

The IBD-Disk questionnaire is the first self-administered and validated questionnaire to evaluate IBD-related disability, with good accuracy and reliability in CD (2,3). The IBD-Disk is a 10-item visual instrument. It is filled out by patients and should allow gastroenterologists to rapidly assess a patient's disability at a given time, but could also be used to follow changes in disease burden over time.

Multiple factors have been associated with high disability, including female gender, perianal location, extra-intestinal manifestations, low level of education, intestinal resection, and hospitalization as well as exposure to anti-TNF, and ethnicity (4–9). In addition, disease activity defined by the Harvey-Bradshaw index (HBI), the physical global assessment (PGA), or biomarkers has been associated with high disability (2).

In the era of the treat-to-target strategy, endoscopic healing has emerged as the goal to achieve, after starting therapy, to prevent intestinal damage and long-term disability. Endoscopic healing is now recognized as one of the main therapeutic targets by the International Organization of Chronic Inflammatory Bowel Diseases (IOIBD) (10) and the European Crohn's and Colitis Organization (ECCO) (11). However, the level of endoscopic healing to achieve is still subject to debate. We recently reported that complete endoscopic healing was associated with better outcomes than partial endoscopic healing in patients with CD (12). However, the level of endoscopic healing needed to achieve lower disability is unknown.

We therefore conducted a prospective multi-center observational study to compare disability associated with complete endoscopic healing to disability with partial endoscopic healing in patients with CD.

## **Methods**

### *Study Population*

We conducted a multicenter prospective observational study in one university hospital (Amiens University Hospital, France), one general hospital (Compiègne Hospital, France), and one private practice center (Polyclinique St.-Claude, Saint Quentin, France). Between September 2019 and November 2020, consecutive patients with CD with endoscopic healing as defined by a Crohn's disease endoscopic index of severity (CDEIS)  $<4$  were included in a prospective cohort. Patients with non-passable ileal or colonic strictures were excluded.

### *Data Collection*

Clinical data, including gender, age at diagnosis, disease location, phenotype according to the Montreal classification, previous and concomitant CD-related medications, smoking status, any history of CD-related surgery, and disease activity according to the Harvey-Bradshaw index (HBI). The IBD-Disk was filled out by each patient on the day of the colonoscopy blind to its results. The IBD-Disk questionnaire includes 0-10 visual analog scales (visual analog scale; 0 = no burden; 10 = maximal burden) assessing each component of disability during the last week. Components are: joint pain, abdominal pain, body image, education and work, emotions, energy, interpersonal interactions, defecation management, sexual function, and sleep. The overall IBD-Disk score was calculated as the sum of its 10 components, ranging from 0 to 100.

### *Definitions and Outcome Measures*

Two definitions of endoscopic healing were compared: complete endoscopic healing defined by a CDEIS of 0 (meaning no signs of active inflammation in any colonic segment or in the terminal ileum) and partial endoscopic healing defined by a CDEIS  $>0$  and  $<4$  (12,13). Moderate to severe disability was defined as an overall IBD-Disk score  $\geq 40$  (3).

### *Statistical Analysis*

Quantitative variables were expressed as median (interquartile range [IQR]), and the qualitative variables were expressed as percentage. Comparison of the quantitative variables with a normal distribution was performed by Student's T-test or by the Wilcoxon rank sum test for variables with a non-normal distribution. For qualitative variables, a  $\chi^2$  test or Fisher exact test was used. A logistic regression model was used to identify factors associated with moderate-to-severe disability expressed as Odds Ratio (OR) (95% confidence interval [CI]). All variables identified with  $P < .10$  were included in a multivariable logistic model. All tests were two-sided, and the threshold for statistical significance was set to  $p < 0.05$  in the final multivariable logistic model. Analyses were performed using R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; [www.r-project.org](http://www.r-project.org)) through the RStudio interface Version 1.3.1093 – © 2009-2020. The protocol was approved, according to national guidelines, by the CNIL committee (Comite Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Sante N°PI2019\_843\_0038).



## Results

### *Study Population*

A total of 82 patients were included. **Table 1** summarizes the main characteristics of the study population. Forty-four (53%) were female and the median age and disease duration were respectively 35.3 years (interquartile range [IQR, 28.6-45.2] and 8.0 years [IQR, 3.0-17.0]). ~~Most patients (n=52, 63.4 %) had inflammatory behavior (B1 Montreal classification), and 34 (41.5%) had an ileocolonic location. Treatment at the time of data collection included infliximab in 38 patients (46.3%), adalimumab in 27 patients (32.9%), vedolizumab in 8 patients (9.8%), ustekinumab in 3 patients (3.7%), and immunomodulator alone in 3 patients (3.7%). Among the patients treated by anti TNF, 30 were in combination therapy. Twenty-two patients (26.8%) had had a previous intestinal resection.~~ Forty-eight (58.5%) had complete endoscopic healing (CDEIS 0), whereas 34 (41.5%) patients had partial endoscopic healing (CDEIS >0 and <4). ~~Baseline characteristics were similar between patient with complete endoscopic healing and those on partial endoscopic healing except for the BMI (Table 1).~~

### *IBD-Disk Overall Score and Subscores*

Among the 82 patients included, the median overall IBD-Disk score was 26.5 (IQR, 9.0-45) and 30 patients (36.6%) had moderate-to-severe disability (overall IBD-Disk score  $\geq 40$ ). The median IBD-Disk score was respectively 24 (IQR, 9.0-40.5) and 34 (IQR, 9.5-51.5) for patients with complete and partial endoscopic healing ( $p=0.068$ ). Respectively, 13/48 (27%) and 17/34 (50%) patients with complete and partial endoscopic healing had moderate to severe disability ( $p=0.039$ ). Item by item, the

median defecation management subscore (0.0 [0.0-3.0] vs 4.0 [0.0-7.5],  $p=0.028$ ) and energy sub score (4.0 [0.0-6.0] vs 6.0 [2.5-8.0],  $p=0.023$ ) were significantly higher in patients with partial endoscopic healing compared to those in complete endoscopic healing (**Table 2, Figures 1-2-S1**).

An IBD-Disk subscore  $>5$  was significantly more frequent in patients with partial mucosal healing for personal interaction ( $p=0.034$ ), and emotion ( $p=0.022$ ) subscores (**Table 3**). Subgroups analysis showed that female patients had significantly higher scores than males for energy ( $p=0.0007$ ), emotion ( $p=0.004$ ), and body image ( $p=0.01$ ) subscores (**Supplementary Figure 1**).

#### *Factors Associated with Disability*

In univariate analysis, female gender, obesity, partial endoscopic healing, and past or active smoking were associated with disability (**Table 4**). In multivariate analysis, partial endoscopic (OR=5.82, 95% CI [1.65, 24.69],  $p=0.0009$ ), female gender (OR=4.0, 95%CI [1.13, 16.58],  $p=0.04$ ), and smoking (OR=8.33, 95% CI [1.96, 50.0]  $p=0.006$ ) were significantly associated with moderate to severe disability.

## Discussion

Disability is the human multidimensional experience of impaired body functions and structures, limited activity, and restricted participation in the interaction with environmental factors. New standards of care, taking into account IBD-related disability and the daily-life burden, are now recommended in clinical practice. Patient-reported outcomes (PROs) are now important endpoints in IBD clinical trials and have been selected as treatment targets (10).

Several factors have been associated with disability, including female gender, perianal location, extra-intestinal manifestations, low level of education, intestinal resection, hospitalization, or ethnicity (4–9). Disease activity defined by the Harvey-Bradshaw index (HBI), the physical global assessment (PGA), or biomarkers has also been associated with high disability (2).

A question remains, could a stricter definition of endoscopic healing be associated with a decrease in disability. To date, no dedicated study has reporting on the impact of different definitions of endoscopic healing on disability. In this study, we observed that patients with CD who achieved complete endoscopic healing defined by CDEIS = 0 had significantly lower disability compared with those having partial endoscopic healing as defined by CDEIS >0 and <4, suggesting that the degree of remission has an impact on global well-being. By exploring IBD-Disk subscores, we observed that a low degree of intestinal inflammation is associated with defecation and energy related disability. Fatigue is frequently reported by patients with IBD and is associated with poor quality of life, disability, and depression. Williet et al. reported that 50% of patients in remission have fatigue, measured with the Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F), and it is correlated with disease activity (9). Borren et al. reported, in a prospective study, that fatigue

improves with initiation of biologic therapy and concomitant resolution of clinical symptoms (14). However, over half of the patients initiating such therapy remain fatigued at 1 year, including one-third of those who are in clinical remission. Fatigue is a complex symptom whose treatment is not codified. Our results suggest, for the first time, that complete endoscopic healing can improve energy, and by analogy, fatigue. Targeting endoscopic activity could be a new way to improve fatigue in CD patients.

These results add to recent findings of our team showing that a stricter definition of endoscopic healing, defined by a CDEIS score of 0, was associated with improved long-term outcomes, including CD-related hospitalizations and surgeries compared to those with partial endoscopic healing defined by a CDEIS  $>0$  and  $<4$  (12). Complete endoscopic healing would therefore be associated with early improvement of disability, but would also reduce the risk of long-term disability by preventing irreversible bowel damage.

Interventional studies are now urgently needed to define a clear cutoff value of endoscopic remission that can be used in clinical trials and in clinical practice for a treat-to-target approach. The present results provide a new argument for using deeper endoscopic healing in clinical remission as a cutoff, as currently discussed in ulcerative colitis, in order to change the disease course and CD-related daily life burden. However, we have to acknowledge that this strategy could be limited by the ability of current drugs to achieve complete endoscopic healing, which has been observed in about 20% of patients included in the CALM study, for example (15). Obtaining complete endoscopic healing would require substantial optimization or change of biologic therapy.

Disability is a complex and multifactorial condition. A high rate of moderate to severe disability was observed in this study despite the inclusion of only patients with endoscopic healing. According to the IBD Disability Index validation study (16), our study confirmed that the IBD Disability Index is associated with female gender. The effects of smoking in CD are well documented as being a risk factor for major outcomes. In terms of disease-specific quality of life, studies show that those who have never smoked have better quality of life compared to former and current smokers. These results were gathered using the short inflammatory bowel disease questionnaire or the health-related quality of life questionnaire (17–19). In the general population, there is a negative relationship between smoking and quality of life (20).

Our study has some limitations. First, there was no centralized reading of endoscopies. Although CDEIS 0 objectively reflects total endoscopic healing, the definition of partial healing may seem arbitrary. This choice is first justified by the fact that the CDEIS is used in daily practice in our centers. Second, a CDEIS lower than 4 is the definition most often used to define endoscopic healing during clinical trials (12,21). Second, level of education, work status, and ethnicity were not investigated, and the medical history of anxiety, depression, or psychological follow-up were not reported. Our study also has many strengths. To our knowledge, this is the first prospective study evaluating the impact of the degree of endoscopic healing on disability in CD. Patients were included consecutively in three different centers. To assess disability, we used a simple and validated tool easily used in daily practice, as well as validated definitions of disability.

In conclusion, complete endoscopic healing (CDEIS = 0) was associated with significantly lower disability than partial endoscopic healing (CDEIS >0 and <4) in

CD. Our findings suggest that deeper endoscopic healing may be needed in clinical practice to reduce the risk of disability in CD.

## **TABLE AND FIGURE LEGENDS**

### **TABLE LEGEND**

**Table 1:** Demographic characteristics of the study population

**Table 2:** Comparison of IBD-Disk subscores using two definitions of endoscopic healing

**Table 3:** Patients with IBD-Disk subscore >5, comparison using two definitions of endoscopic healing

**Table 4:** Univariate and multivariate analysis of factors associated with disability

### **FIGURE LEGEND**

**Figure 1:** Comparison of median IBD-Disk subscores using two definitions of mucosal healing.

**Figure 2 :** Influence of complete mucosal healing (CMH) and partial mucosal healing (PMH) on IBD subscores, box plot analysis

## **References**

- [1] Casellas F, Barreiro de Acosta M, Iglesias M, Robles V, Nos P, Aguas M, et al. Mucosal healing restores normal health and quality of life in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2012;24:762–9. <https://doi.org/10.1097/MEG.0b013e32835414b2>.
- [2] Le Berre C, Flamant M, Bouguen G, Siproudhis L, Dewitte M, Dib N, et al. VALIDation of the IBD-Disk Instrument for Assessing Disability in Inflammatory Bowel Diseases in a French Cohort: The VALIDate Study. *Journal of Crohn's and Colitis* 2020;14:1512–23. <https://doi.org/10.1093/ecco-jcc/jjaa100>.
- [3] Tadbiri S, Nachury M, Bouhnik Y, Serrero M, Hébuterne X, Roblin X, et al. The IBD-disk Is a Reliable Tool to Assess the Daily-life Burden of Patients with Inflammatory Bowel Disease. *Journal of Crohn's and Colitis* 2020;jjaa244. <https://doi.org/10.1093/ecco-jcc/jjaa244>.
- [4] Lauriot dit Prevost C, Azahaf M, Nachury M, Branche J, Gerard R, Wils P, et al. Bowel damage and disability in Crohn's disease: a prospective study in a tertiary referral centre of the Lémann Index and Inflammatory Bowel Disease Disability Index. *Aliment Pharmacol Ther* 2020;51:889–98. <https://doi.org/10.1111/apt.15681>.
- [5] Marinelli C, Savarino E, Inferrera M, Lorenzon G, Rigo A, Ghisa M, et al. Factors Influencing Disability and Quality of Life during Treatment: A Cross-Sectional Study on IBD Patients. *Gastroenterology Research and Practice* 2019;2019:1–10. <https://doi.org/10.1155/2019/5354320>.
- [6] Costa JM, Matos D, Arroja B, Gonçalves R, Soares JB. The main determinants of disability in IBD and its relationship to optimism. *Rev Esp Enferm Dig* 2019;111. <https://doi.org/10.17235/reed.2019.6033/2018>.
- [7] Shafer LA, Walker JR, Chhibba T, Targownik LE, Singh H, Ivekovic M, et al. Health Care Indicators of Moderate to Severe IBD and Subsequent IBD-Related Disability: A Longitudinal Study. *Inflammatory Bowel Diseases* 2019;25:1996–2005. <https://doi.org/10.1093/ibd/izz102>.
- [8] Agrawal M, Cohen-Mekelburg S, Kayal M, Axelrad J, Galati J, Tricomi B, et al. Disability in inflammatory bowel disease patients is associated with race, ethnicity and socio-economic factors. *Aliment Pharmacol Ther* 2019;49:564–71. <https://doi.org/10.1111/apt.15107>.
- [9] Williet N, Sarter H, Gower-Rousseau C, Adrianjafy C, Olympie A, Buisson A, et al. Patient-reported Outcomes in a French Nationwide Survey of Inflammatory Bowel Disease Patients. *ECCOJC* 2017;11:165–74. <https://doi.org/10.1093/ecco-jcc/jjw145>.



- [10] Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021;160:1570–83. <https://doi.org/10.1053/j.gastro.2020.12.031>.
- [11] Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detections of complications. *Journal of Crohn's and Colitis* 2018. <https://doi.org/10.1093/ecco-jcc/jjy113>.
- [12] Yzet C, Diouf M, Le Mouel J-P, Brazier F, Turpin J, Loreau J, et al. Complete Endoscopic Healing Associated With Better Outcomes Than Partial Endoscopic Healing in Patients With Crohn's Disease. *Clinical Gastroenterology and Hepatology* 2019. <https://doi.org/10.1016/j.cgh.2019.11.025>.
- [13] Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989;30:983–9. <https://doi.org/10.1136/gut.30.7.983>.
- [14] Borren NZ, Tan W, Colizzo FP, Luther J, Garber JJ, Khalili H, et al. Longitudinal Trajectory of Fatigue With Initiation of Biologic Therapy in Inflammatory Bowel Diseases: A Prospective Cohort Study. *Journal of Crohn's and Colitis* 2020;14:309–15. <https://doi.org/10.1093/ecco-jcc/jjz148>.
- [15] Colombel J-F, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2018;390:2779–89. [https://doi.org/10.1016/S0140-6736\(17\)32641-7](https://doi.org/10.1016/S0140-6736(17)32641-7).
- [16] Gower-Rousseau C, Sarter H, Savoye G, Tavernier N, Fumery M, Sandborn WJ, et al. Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. *Gut* 2017;66:588–96. <https://doi.org/10.1136/gutjnl-2015-310151>.
- [17] Quezada S, Langenberg P, Cross R. Cigarette smoking adversely affects disease activity and disease-specific quality of life in patients with Crohn's disease at a tertiary referral center. *CEG* 2016;Volume 9:307–10. <https://doi.org/10.2147/CEG.S104652>.
- [18] Russel MG, Nieman FH, Bergers JM, Stockbrügger RW. Cigarette smoking and quality of life in patients with inflammatory bowel disease: *European Journal of Gastroenterology & Hepatology* 1996;8:1075–81. <https://doi.org/10.1097/00042737-199611000-00009>.
- [19] Severs M, Mangen M-JJ, van der Valk ME, Fidder HH, Dijkstra G, van der Have M, et al. Smoking is Associated with Higher Disease-related Costs and Lower

Health-related Quality of Life in Inflammatory Bowel Disease. ECCOJC 2016;jjw160. <https://doi.org/10.1093/ecco-jcc/jjw160>.

[20] Goldenberg M, Danovitch I, IsHak WW. Quality of life and smoking: Quality of Life and Smoking. *Am J Addict* 2014;23:540–62. <https://doi.org/10.1111/j.1521-0391.2014.12148.x>.

[21] Ma C, Hussein IM, Al-Abbar YJ, Panaccione R, Fedorak RN, Parker CE, et al. Heterogeneity in Definitions of Efficacy and Safety Endpoints for Clinical Trials of Crohn's Disease: A Systematic Review. *Clinical Gastroenterology and Hepatology* 2018. <https://doi.org/10.1016/j.cgh.2018.02.051>.

<b>Characteristics</b>	<b>CDEIS 0 (n = 48)</b>	<b>CDEIS &gt;0 &lt;4 (n = 34)</b>	<b>p-Value</b>
<b>Age at diagnosis, years</b> (median, IQR)	25.0 (20.0 – 29.2)	24.4 5 (20.0-35.0)	0.901
<b>Female, n (%)</b>	21 (43.7)	23 (67.6)	0.311
<b>BMI, kg/m<sup>2</sup></b> (median, IQR)	22.9 (20.8-25.9)	25.1 (23.0-31.1)-	<b>0.004</b>
<b>Tobacco status, n (%)</b>			0.684
Never	14 (29.1)	12 (35.2)	
Former	14 (29.1)	11 (32.3)	
Current	20 (41.6)	11 (32.3)	
<b>Disease duration</b>	10.25 (9.14)	12.06 (10.98)	0.419
<b>Phenotype of the CD according to Montreal classification, n (%)</b>			0.458
B1	31 (64.5)	21 (61.7)	
B2	8 (16.6)	9 (26.4)	
B3	9 (18.7)	4 (11.7)	
<b>Location of CD according to Montreal classification, n (%)</b>			0.906
L1	15 (31.2)	12 (35.2)	
L2	13 (27.1)	7 (20.6)	
L3	20 (41.6)	14 (41.1)	
L4	6 (12.5)	4 (11.7)	
<b>Perianal involvement</b> (n, %)	12 (25.0)	7 (20.5)	0.841
<b>History of intestinal resection, n (%)</b>	10 (20.8)	12 (35.2)	0.229
<b>Number of biologics used</b> (median [IQR])	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.347
<b>Current treatment, n (%)</b>			
Adalimumab	14 (29.1)	13 (40.6)	0.476
Infliximab	26 (54.1)	12 (37.5)	0.117
Vedolizumab	4 (8.3)	3 (9.3)	1.0
Ustekinumab	1 (2.1)	2 (6.2)	0.567
Others	3 (6.2)	2 (6.2)	1.0
<b>Biomarkers</b> (median, IQR)			
CRP (mg/L)	1.4 (1.0 – 2.0)	5.0 (2.5-5.5)	<b>0.049</b>
Calprotectin (ug/g)	94 (21-176)	114 (34-191)	0.32

**Table 1:** Demographic characteristics of the study population. CD, Crohn's disease ; BMI, Body mass index

	<b>CDEIS 0</b> <b>(n = 48)</b>	<b>CDEIS &gt;0 &lt;4</b> <b>(n = 34)</b>	<b>p</b>
<b>Joint pain</b> (median, IQR)	1.00 [0.00, 5.00]	4.00 [0.00, 6.00]	0.069
<b>Abdominal pain</b> (median, IQR)	2.00 [0.00, 5.00]	2.00 [0.00, 6.50]	0.456
<b>Regulating defecation</b> (median, IQR)	0.00 [0.00, 3.00]	4.00 [0.00, 7.50]	<b>0.028</b>
<b>Interpersonal interactions</b> (median, IQR)	0.00 [0.00, 1.00]	0.00 [0.00, 5.50]	0.097
<b>Education and work</b> (median, IQR)	0.00 [0.00, 3.00]	4.00 [0.00, 7.00]	0.061
<b>Sleep</b> (median, IQR)	2.00 [0.00, 6.00]	4.00 [0.00, 7.50]	0.421
<b>Energy</b> (median, IQR)	4.00 [0.00, 6.00]	6.00 [2.50, 8.00]	<b>0.023</b>
<b>Emotions</b> (median, IQR)	1.00 [0.00, 5.00]	4.00 [0.00, 8.00]	0.144
<b>Body image</b> (median, IQR)	1.00 [0.00, 5.00]	1.00 [0.00, 5.00]	0.883
<b>Sexual functions</b> (median, IQR)	0.00 [0.00, 3.00]	0.00 [0.00, 3.00]	0.975

**Table 2:** Comparison of IBD-Disk subscores using two definitions of endoscopic healing. CDEIS, Crohn's disease endoscopic index of severity ; IQR, Interquartile range.

<b>Patients with IBD-Disk subscore &gt;5</b>	<b>Overall study population (n = 82)</b>	<b>CDEIS 0 (n = 48)</b>	<b>CDEIS &gt;0 &lt;4 (n = 34)</b>	<b>p</b>
<b>Joint pain, n (%)</b>	23 (28.0%)	10 (20.8%)	13 (38.2%)	0.13
<b>Abdominal pain, n (%)</b>	21 (25.6%)	10 (20.8%)	11 (32.3%)	0.31
<b>Regulating defecation, n (%)</b>	21 (25.6%)	8 (16.7%)	13 (38.2%)	0.12
<b>Interpersonal interactions, n (%)</b>	13 (15.8%)	4 (8.3%)	9 (26.4%)	<b>0.034</b>
<b>Education and work, n (%)</b>	18 (21.9%)	7 (14.6%)	11 (32.3%)	0.064
<b>Sleep, n (%)</b>	27 (32.9%)	13 (27.0%)	14 (41.2%)	0.23
<b>Energy, n (%)</b>	33 (40.2%)	15 (31.2%)	18 (52.9%)	0.067
<b>Emotions, n (%)</b>	22 (26.8%)	8 (16.7%)	14 (41.2%)	<b>0.022</b>
<b>Body image, n (%)</b>	19 (23.1%)	12 (25.0%)	7(20.6%)	0.79
<b>Sexual functions, n (%)</b>	12 (14.6%)	5 (10.4%)	7 (20.6%)	0.22

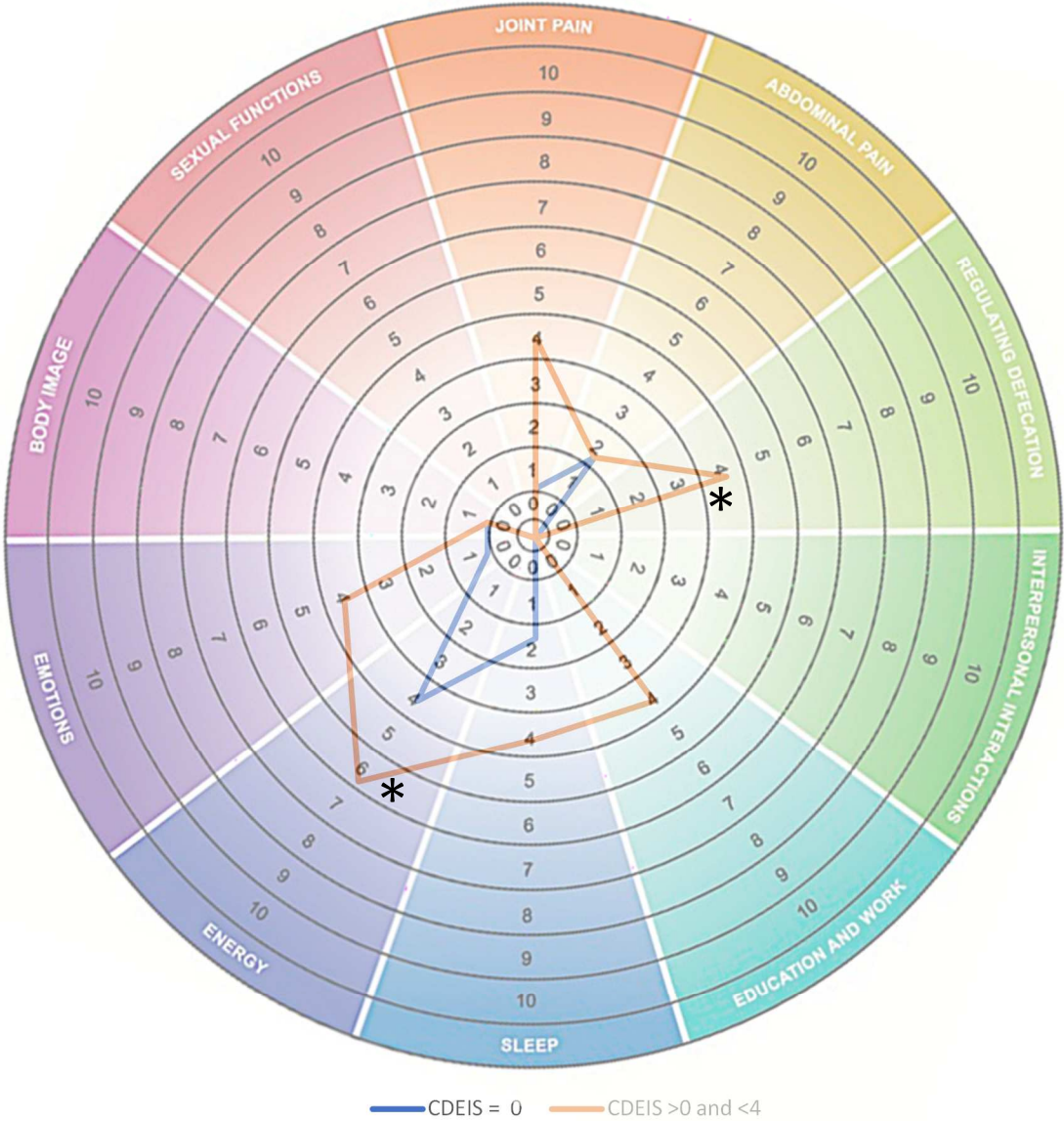
**Table 3:** Patients with an IBD-Disk subscore >5 with two definitions of endoscopic healing. CDEIS, Crohn's disease endoscopic index of severity

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
<b>CDEIS (&gt;0 &lt;4 vs. 0)</b>	<b>2.69 [1.08, 6.93]</b>	<b>0.036</b>	<b>5.82 [1.65, 24.69]</b>	<b>0.009</b>
Age at diagnosis	0.99 [0.95, 1.04]	0.763		
<b>Sex (F vs M)</b>	<b>3.75 [1.45, 10.45]</b>	<b>0.008</b>	<b>4.00 [1.13, 16.58]</b>	<b>0.040</b>
<b>BMI*</b>	<b>1.10 [1.02, 1.22]</b>	<b>0.028</b>		
<b>Tobacco status</b>				
Former vs. current	<b>0.32 [0.10, 0.96]</b>	<b>0.047</b>	<b>0.16 [0.03, 0.69]</b>	<b>0.021</b>
Never vs. current	<b>0.25 [0.07, 0.75]</b>	<b>0.018</b>	<b>0.12 [0.02, 0.51]</b>	<b>0.006</b>
<b>Phenotype</b>				
2 vs. 1	2.12 [0.70, 6.60]	0.183		
3 vs. 1	0.57 [0.12, 2.13]	0.430		
<b>Location</b>				
2 vs. 1	0.69 [0.19, 2.34]	0.551		
3 vs. 1	1.13 [0.38, 3.38]	0.825		
Biologics number	2.32 [1.34, 4.54]	0.006	<b>2.31 [1.24, 4.91]</b>	<b>0.014</b>
Duration of disease	0.99 [0.94 ; 1.03]	0.562	<b>0.94 [0.87; 1.01]</b>	<b>0.116</b>

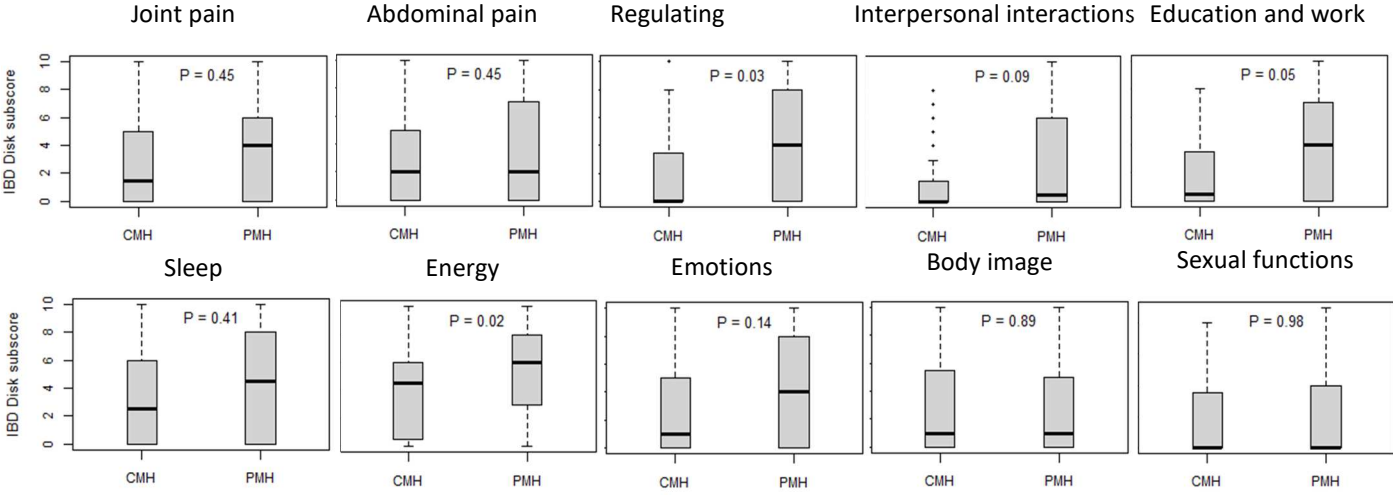
**Table 4:** Univariate and multivariate analysis of factors associated with disability. OR, Odds Ratio; CDEIS, Crohn's disease endoscopic index of severity.

\*BMI didn't enter the multivariable model due to its multicollinearity with CDEIS and in order to achieve an acceptable number of events per variable

**Figure 1:** Median IBD-Disk subscores in patients with complete endoscopic healing (blue) and partial endoscopic healing (red)



**Figure 2:** Influence of complete mucosal healing (CMH) and partial mucosal healing (PMH) on IBD-Disk subscores, box plot analysis





**Supplementary Figure 1** : IBD-Disk subscores according to gender, box plot analysis

