

Inflammatory bowel diseases and work disability: a systematic review of predictive factors

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Abstract. – **OBJECTIVE:** Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and Ulcerative Colitis (UC), are chronic, relapsing intestinal disorders that may severely compromise patients' labour force participation. In this context, the present review aims to provide an overview on possible IBD pathological, socio-demographic, and treatment-related factors predictive for work disability with the purpose to provide guidance for a successful clinical and occupational management.

MATERIALS AND METHODS: A systematic review of PubMed, Scopus, and ISI Web of Science databases was performed to retrieve all the studies addressing IBD-related predictors for work disability.

RESULTS: Several factors have been suggested to predict work disability in the 15 revised investigations, although with not homogeneous results. Having CD was reported as a significantly better predictor for permanent work disability compared to UC, maybe in relation to the generally more serious disease course. Activity and severity of IBD, also indicated by the need for surgical treatment and comorbidities, was related to a significantly greater risk for work disability, although the exact role of other variables, i.e., specific symptoms, disease pattern and inflammatory parameters are still unclear. Among demographic factors, a significant predictive role has been suggested for female gender.

CONCLUSIONS: Further research seems necessary to confirm the role of IBD related factors on work disability, and on other parameters of work impairment, i.e., absenteeism, presenteeism, activity and productivity loss. Additionally, work disability should be evaluated in relation to specific occupational risk factors. Overall, this may require a multidisciplinary approach aimed to achieve an adequate IBD clinical evaluation and management, an improvement of patients' psychosocial and professional well-being, while appropriately assessing and managing risks in the workplace.

Key Words:

Inflammatory bowel diseases, Crohn's disease, Ulcerative colitis, Work disability, Disability pension, Predictive factors.

Introduction

Inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and Ulcerative Colitis (UC), are lifelong disorders characterized by chronic relapsing of intestinal inflammation^{1,2}. Patients generally suffer from symptoms like abdominal pain, rectal bleeding, diarrhea, fatigue and weight loss that can impact every dimension of the affected individual's life³⁻⁵. Additionally, some patients may experience intestinal and extra-intestinal complications, including peripheral arthropathy, skin and eye manifestations⁶⁻⁹. The disease course is unpredictable, and may be complicated by flares, and need for chronic therapies, hospital admissions, and surgery¹⁰⁻¹².

More than 2 million Europeans and 1.5 million North Americans have IBD¹³. Inflammatory bowel disease is more common in developed countries, with the highest incidence rates being reported in the Northern and Western Europe, as well as in the North America, with a recent increasing trend in Asian populations^{14,15}. Although it can affect patients at any age, it primarily occurs in young individuals, with an average age of onset in adults between 31 and 34 years with a peak in the age range of 20-30 years¹⁶.

Due to the early age of onset, disease chronicity, persistent activity, repeated flares, as well as the need for hospital admissions, medical and surgical treatment, IBD may affect the quality of life and "labor force" participation of patients. In fact, they may be severely compromised at work, with unemployment or early retirement, multiple sick leave, and work capacity impairments, up to work disability^{17,18}. This latter may include a physical impairment, an activity limitation or a participation restriction and represents the result of the complex interplay between individual health conditions

and the features of the “occupational environment” in which he or she works, particularly as regards experienced occupational risk factors¹⁹.

However, although the impact of CD and/or UC on work ability has been the object of numerous investigations²⁰⁻²⁹, available data on the prevalence of work disability are still heterogeneous. In fact, the overall prevalence of the phenomenon ranges from 1.3% to 50%^{20,22-24,27,28,30-34}, depending on the sample size, the investigated population, and the study design, also concerning the time periods in which the studies were carried out, as well as the diverse socioeconomic settings between countries, i.e., differences in social security systems, employment rates, and in the definitions of disability^{35,36}.

Importantly, considering the global burden of the disease, IBD work disability may be associated with high societal costs, especially if it develops at a young age and acquires a permanent nature^{32,37}. Therefore, its prevention is an important goal in the disease management, taking also into account that, over the last decades, the successful IBD treatment moved from the induction and maintenance of clinical remission, to the prevention of structural damage and long-term disability. In this perspective, it seems essential, not only to define the prevalence of work disability in IBD populations, but also to deeply understand the function of possible predictive factors. Work disability, in fact, has been generally related to the severity of IBD and to disease related aspects, but the roles of other factors, such as age, sex or educational level, still remain controversial³⁸.

Therefore, the aim of this review was to provide an overview on possible predictive factors for temporary or permanent disability, with different grade of severity, in IBD patients with a specific focus on socio-demographical, pathological, and treatment-related modifier factors. To gain deep insight into the role of such issues on work disability may provide guidance to plan suitable, comprehensive, disease management strategies. This may support a multidisciplinary approach to guarantee patients a key success in the control of clinical symptoms, as well an “active” labor force participation, including the employment integration and job maintenance. Overall, this may enable IBD patients to achieve a fulfilling quality of life, social contacts and self-esteem, therefore supporting their psycho-social and professional

well-being, while reducing work disability, productivity loss, as well as the direct and indirect societal costs of the disease.

Materials and Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria³⁹, a systematic literature search was performed on PubMed, Scopus, and ISI Web of Science databases in order to retrieve all the articles investigating predictive factors for work disability in IBD patients and published from 2000 up to the 8th September 2020. The search terms used were (“inflammatory bowel disease*” or “Crohn’s disease” or “Ulcerative Colitis”) AND (“work disability”) AND (“predictive factor*” or “predictor*”). All the titles and abstracts retrieved by the computerized search were independently reviewed by two of the authors who selected the papers that could be considered relevant for the review purposes, in accordance with the inclusion criteria. These included peer-reviewed research articles, i.e., cross-sectional, cohort, case-control studies, are published in English. Studies had to explore socio-demographical, pathological, as well as treatment-related issues that may function as predictive factors for work disability in IBD patients. Articles published in languages other than English, case studies, review, editorials and conference papers, as well as studies addressing disability, not specifically referred to the occupational setting, those failing to report possible predictors for work disability or focused on occupational outcomes diverse from work disability, i.e., sick leave, loss of productivity, activity impairments, were excluded.

A methodological critical evaluation of each individual study was performed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies^{40,41}. In case of disagreement between the two reviewers, remaining authors also reviewed the article, and the judgement made by the majority of the reviewers determined the quality rating. In the case of cohort and case-control studies, the NOS contains 8 items, categorized into three dimensions, including selection, comparability, and, depending on the study type, outcome (cohort studies) or exposure (case-control studies). The NOS score ranges from 0 up to 9. To perform a quality assessment of cross-sectional studies, a NOS adapted for this kind of investigations has been employed. Adapt-

ed NOS assesses the risk of bias in 3 comparable areas: selection, comparability and outcome, and has a score that ranges for 0 to 10 points. The quality assessment of the studies was rated as follows: very good (9, 10 points), good (7, 8 points), satisfactory (5, 6 points), unsatisfactory (0-4 points).

Results

The search retrieved 8, 10 and 15 references through PubMed, Scopus and ISI Web of Science databases, respectively, for a total of 33 articles (Figure 1). Sixteen duplicates were removed from the total number of papers. Out of the remaining 17 articles, studies that did not meet the inclusion criteria were excluded according to the following reasons: 10 were out of the topic from the title and

abstract analysis and 1 was excluded as review article. Indeed, a total of 6 publications remained for review. All the full texts of the articles that were considered suitable for review were obtained and subjected to a critical evaluation. The assessment of the reference list accompanying the selected papers further enlarged the citation pool of relevant publications that were identified in the literature search. This allowed for the inclusion of 9 additional eligible papers. Overall, our search retrieved a total of 15 articles for review whose designs, findings and quality rating have been described in Table I. The following paragraphs will attempt to summarise the results of the studies on possible variables categorized into disease-related factors, treatment related-modifiers, and socio-demographic features that could have a predicting role for work disability in IBD patients.

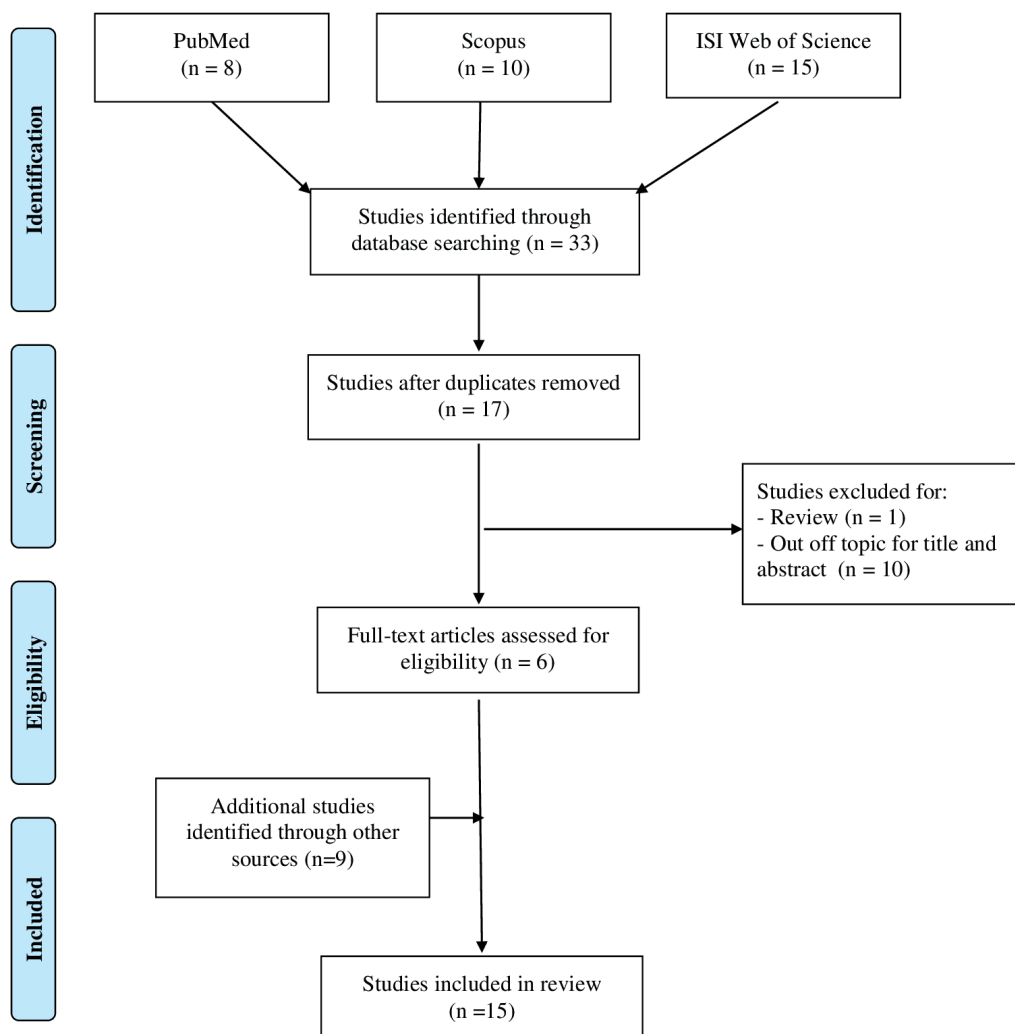


Figure 1. Flow diagram of literature search.

Table I. Summary of the studies addressing predictive factors for work disability in IBD affected patients.

Study location (period of investigation)	Study design	Population	Disability rate	Predictive Factors of work disability	Quality Rating According to NOS	Ref.
Netherlands (2000)	Case-Control study	Total IBD population No. 680 (female No. 369); UC patients No. 359 (mean±SD age: 43.6 ±11 y); CD patients No. 282 (mean±SD age: 37.3±11y); Indeterminate colitis No. 39 Control population: No. 715 (female No. 359; mean±SD age: 42.5±11y)	<i>Chronic work disability rate:</i> No. 85 (24%) UC patients; No. 90 (32%) CD patients No. 188 (28%) IBD population; No. 75 (10.5 %) controls population. <i>Partial work disability rate:</i> No. 38 (10.5%) UC patients; No. 24 (8.5%) CD patients; No. 67 (9.8%) IBD population; No. 28 (3.9%) controls population. <i>Full Work disability:</i> No. 49 (13.5%) UC patients; No. 66 (23%) CD patients; No. 123 (18%) IBD population; No. 47 (6.5%) control population.	Significant predictors for work disability: ✓ IBD type: UC vs. CD (OR: 0.51, 95% CI 0.34-0.77); ✓ Disease course (OR for only one lifetime episode of disease vs. continuous disease activity 0.11, 95% CI 0.06-0.22; recurring episodes of disease vs. continuous disease activity: 0.3, 95% CI 0.2-0.4); ✓ Low education (OR for low vs high education: 3.8, 95% CI 2.4-6.2; OR for middle education vs. high education: 2.7, 95% CI 1.7-4.3).	Very Good	Boonen et al ²³
Norway (1990-1998)	Cohort study	Total IBD population No. 495 (female No. 243; mean±SD age: 41.2 ±13.7 y); UC patients No. 334; CD patients No. 161.	<i>Disability pension rate:</i> No. 42 IBD patients (8.5%) [No. 16 (6.3%) male; No. 26, 10.7% female]; No. 24 (14.9%) CD patients [No. 7 (8.5%) CD male patients; No. 17 (24.6%) CD female patients]; No. 18 (5.4%) UC patients [No. 9 (5.5%) UC male patients; No. 9 (5.2%) UC female patients].	<i>Significant predictive factors for disability:</i> ✓ IBD type: CD>UC; ✓ Female gender (only CD patients); ✓ Young age.	Good	Bernklev et al ²²

Table continued

Table I. (Continued). Summary of the studies addressing predictive factors for work disability in IBD affected patients.

Study location (period of investigation)	Study design	Population	Disability rate	Predictive Factors of work disability	Quality Rating According to NOS	Ref.
Usa	Case-control study	CD population No. 185 (female No. 23; average age of 42.8 y). Patients receiving social security disability: No. 39 (5.3%); mean±SD age: 45.8 ±10.4 y. Control population: 148 (female No. 80; mean±SD age: 42.0 ± 15.0 y)	Mean quality of life scores (SIB-DQ): disabled CD patients: 40.4 ± 11.5; controls: 54.6 ± 9.3.	<i>Significant predictive factors for disability:</i> ✓ Undergoing ≥ 2 gastrointestinal surgeries (OR 7.09, 95% CI 2.63-19.11); ✓ Undergoing ≥ 2 medical hospitalization (OR 2.76, 95%CI 1.03- 7.37).	Good	Ananthakrishnan et al ²⁰
Sweden (1999-2001)	Cohort study	Total IBD population No. 781 (female No. 420); UC patients No. 284 (median age: 46 y range: 36-58); CD patients No. 497 (median age: 46 y range: 33-56)	<i>Labour force participation rate:</i> 65.7% CD population; 81.3% background population. <i>Disability pension rate:</i> significantly increased in IBD patients (15.2%) compared to the general population (19.2% in female and 11.3 % in male patients)	<i>Significant predictive factors for disability:</i> ✓ Female gender (OR 2.34, 95% CI: 1.24-3.66); ✓ Older age (OR: 1.07, 95% CI: 1.04-1.11); ✓ Concomitant disease (OR: 2.78, 95% CI: 1.50-4.33); ✓ Disease course in the preceding year (OR 2.12, 95% CI: 1.24-3.66).	Good	Stjernman et al ⁴¹
Norway (1990-2003)	Cohort	Total IBD population No. 501 (female No. 251); UC patients No. 341 (median age: 45.6, range: 22.2-76) CD patients No. 160 (median age: 38.1, range: 19.1-74.6)	<i>Overall work disability rate:</i> No. 94 (18.8%) for the total population of IBD patients. There was no difference in the disability rate between CD and UC. <i>Work disability rate due to IBD:</i> No. 32 (9.4%) UC patients; No. 25 (15.6%) CD patients. <i>Work disability rate for other causes:</i> No. 31 (9.1%) UC patients; No. 6 (3.8%) CD patients. <i>Relative Risk of Disability pension in the 10 years after disease onset:</i> 1.8 (95%-CI: 1.4-2.3) UC patients; 2.0 (95%-CI: 1.4-2.7) CD patients.	<i>Significant predictors work disability:</i> ✓ Female gender (RR 95% CI): UC:1.83 (1.34-2.44); CD: 2.47 (1.69-3.44); ✓ Steroid treatment (OR 95% CI): UC: 5.46 (2.37-12.59); CD: 4.33 (1.96-9.59); ✓ Increased CRP or ESR at diagnosis (OR 95% CI): only UC: 2.49 (1.20-5.16); ✓ Early colectomy (OR 95% CI): only UC: 4.82 (1.65-14.1); ✓ More than 2 relapses during the first year of the disease: only UC: 3.68 (1.45 -9.35).	Very Good	Høivik et al ²⁷

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Table I. (Continued). Summary of the studies addressing predictive factors for work disability in IBD affected patients.

Study location (period of investigation)	Study design	Population	Disability rate	Predictive Factors of work disability	Quality Rating According to NOS	Ref.
Switzerland (2003-2006)	Cohort study	Total IBD population No. 1187 (female No. 622); UC patients No. 488 (mean±SD age: 42.6 ±13.9 y); CD patients No. 699 (mean±SD age: 41.8±14.7y)	<i>Permanent disability:</i> No. 479 (3.1%) UC patients; No. 659 (9.7%) CD patients at enrollment; No. 307 (1.6%) UC patients; No. 412 (1.7%) CD patients during follow up <i>Temporary disability:</i> No. 433 (21.3%) UC patients; No. 600 (19.3%) CD patients at enrollment; No. 286 (12.6%) UC patients; No. 401 (12.2%) CD patients during follow-up.	<i>Significant predictive factors for disability:</i> Temporary disability (OR; 95% CI): ✓ Female: 2.49 (1.11-5.55) only CD; ✓ Disease activity: 5.23 (1.83-14.99) UC; 4.75 (1.83-12.34) CD; Permanent disability (OR; 95% CI): ✓ Disease activity: 29.04 (2.36-357.41) UC; 2.26 (1.57-3.25) CD.	Very Good	Siebert et al ³⁴
Hungary (2012-2013)	Cohort study	Total IBD population No. 443 (female No. 241); UC patients No. 183 (mean±SD age: 30 ±13 y); CD patients No. 260 (mean±SD age: 26.3±11.2 y)	<i>Disability Pension rate:</i> No. 143 (32.3 %) IBD population (IBD related: 88.8%). <i>Partial Disability Pension rate:</i> No. 107 (24.2 %) IBD population. <i>IBD related Disability pension</i> (overall cases of disability pension): No. 222 (88.8 %) <i>Full Disability Pension prevalence:</i> full disability pension was significantly more prevalent in IBD population [No. 36 (8.1 %)] and CD population [No. 24 (9.2 %)], but not in UC patients [No. 12 (6.6 %)] compared to the background population, 5.5%. <i>Work productivity impairment in employed patients:</i> absenteeism: 25.9%; presenteeism: 60.3%; loss of work productivity: 28%; activity loss: 32%.	<i>Significant predictive factors for disability in CD patients:</i> ✓ Younger age (OR 95%CI): <35 y: 12.2 (5.59-26.7); 36-40 y: 7.79 (3.67-16.6); 41-45 y: 7.4 (3.38-16.2); > 46 y: no increased risk; ✓ Previous surgery or colectomy (OR 5.40, 95% CI 3.10-9.41); ✓ Arthritis/arthritis (OR 3.41, 95% CI 1.98- 5.89).	Satisfactory	Mandel et al ²⁹
Canada (2002- 2014)	Cohort study	UC patients No. 119 (mean±SD age: 52.1 ±14.3 y); CD patients No. 125 (mean±SD age: 46.5.1±14.2 y)	<i>Work disability rate:</i> significantly higher disability rate assessed through the Work and Social Adjustment Scale (score > 17) in CD patients (19%) compared to UC patients (11%)	<i>Significant predictors for work disability:</i> ✓ Long term disease activity: Only CD OR: 7.69; 95% CI: 1.99- 29.61.	Good	Israeli et al ¹⁹

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Table I. (Continued). Summary of the studies addressing predictive factors for work disability in IBD affected patients.

Study location (period of investigation)	Study design	Population	Disability rate	Predictive Factors of work disability	Quality Rating According to NOS	Ref.
Netherlands (2010-2013)	Cohort study	Total IBD population No. 2282 (female No. 1413); UC patients No. 909 (mean±SD age: 46.1 ±11.4 y); CD patients No. 1373 (mean±SD age: 44.1±11.8 y)	<i>Work disability:</i> significantly higher rates of work disability were reported for CD compared to UC patients. A total of No. 251 (18.3%) CD patients were fully disabled (>80%, these patients are entitled to an income replacing disability benefit); No. 121 (8.8%) CD patients were partially disabled (> 35%, but not fully); No. 86 (9.5%) UC patients were fully disabled; No. 49 (5.4%) UC patients were partially disabled.	<i>Significant predictors for work disability (OR, 95% CI):</i> ✓ Older age: UC: 4.31 (2.24-8.30); CD: 3.44 (2.15-5.51); ✓ Female gender: only CD: 1.55 (1.13-2.13); ✓ Low education: CD: 2.63 (1.90-3.65); UC: 1.77 (1.14-2.76); ✓ Abdominal surgery: UC: 3.62 (2.01-6.52); CD: 1.57 (1.12-2.19); ✓ Depression: UC: 2.25 (1.23-4.11); CD: 1.92 (1.19-3.10); ✓ Chronic back pain, joint manifestations: UC: 2.51 (1.31-4.83), 2.27 (1.36-3.78), respectively; CD: 2.47 (1.55-3.94), 2.60 (1.84-3.69), respectively; ✓ Previous use of corticosteroids: only UC: 2.43 (1.49-3.96); ✓ Penetrating disease: only CD: 1.47 (0.94-2.30); ✓ Impaired body function: only CD: 1.60 (1.07-2.39); Stoma: only CD: 1.55 (1.13-2.13).	Satisfactory	Van der Valk et al ²⁸
Spain (2012-2013)	Cross sectional study	Total IBD population (No. 293); UC patients No. 142 (mean±SD age: 43.1±11 y); CD patients No. 151 (mean±SD age: 48±10.2 y)	<i>Employment status:</i> No. 214 (73%) IBD patients were employed; No. 16 (5.5%) unemployed; No. 11(3.8%) prematurely retired; No. 30 (%) homemakers; No. 10 (%) students. <i>Work disability:</i> No. 12 (4.1%) received a work-disability pension; No. 93 (32%) any officially recognized disability; No. 73 (25%) moderate disability; No. 16 (5%) severe disability.	<i>Significant predictors for any grade of disability in multivariate analysis:</i> ✓ Anti-TNF drug; ✓ Number of previous surgeries; ✓ Number of diagnostic studies the previous year. <i>Significant predictors of severe disability (with disability pension) in univariate analysis:</i> ✓ Older age; ✓ IBD activity; ✓ Anti-TNF drug; ✓ Ileostomy/coleostomy; ✓ Fecal incontinence.	Satisfactory	Ramos et al ⁴³

Table continued

Table I. (Continued). Summary of the studies addressing predictive factors for work disability in IBD affected patients.

Study location (period of investigation)	Study design	Population	Disability rate	Predictive Factors of work disability	Quality Rating According to NOS	Ref.
Norway (2003-2011)	Case-control	Total IBD population No. 379 (female No. 193); UC patients No. 224; CD patients No. 155; Control population No. 1435 (female: No. 737)	<p><i>Work Disability rate:</i> No. 13 (5.8%) UC patients; No. 9 (5.8%) CD patients; No. 45 (3.1%) control population.</p> <p><i>Hazard ratio of Work Disability with respect to the overall background population (HR 95% CI):</i> 2.1 (1.2-3.8) IBD; 2.7 (1.2-6.2) UC; 1.6 (0.7-3.8) CD patients.</p>	<p><i>Significant predictors work disability (HR, 95% CI):</i></p> <ul style="list-style-type: none"> ✓ IBD subtype: CD (HR 2.7; 95% CI 1.2-6.2); UC (HR 1.6; 35% CI 0.7-3.8); ✓ Male gender (HR 2.5; 95% CI 1.1-5.7); ✓ Age >55 y at diagnosis: (HR 7.2, 95% CI 2.0-25.7). 	Very Good	Vester Andersen et al ⁴⁵
Netherlands (2007)	Cohort study	Total IBD population No. 2794 (female No. 1655); UC patients No. 1054 (median age: 43.4y, range: 33-53); CD patients No. 1740 (median age: 39.9 y, range: 30-51).	<p><i>Employment status:</i> full-time: No. 440 (42%) UC patients; No. 607 (35%) CD patients; <i>part-time:</i> No. 224 (21%) UC patients; No. 359 (21%) CD patients;</p> <p><i>High Work disability rate:</i> No. 200 (19%) UC patients; No. 505 (29%) CD patients; 7% general Dutch population.</p> <p><i>Work disability: Partial (35-80% work disability for > 2 y):</i> No. 54 (5%) UC patients; No. 129 (7%) CD patients; <i>Full (> 80% work disability for > 2 years):</i> No. 124 (12%) UC patients; No. 342 (20%) CD patients; <i>Sick leave (work disability for <2 y):</i> No. 36 (3%) UC patients; No. 77 (4%) CD patients; <i>Retired:</i> No. 21 (2%) UC patients; No. 22 (1.3%) CD patients; <i>Other:</i> No. 155 (15%) UC patients; No. 204 (12%) CD patients.</p>	<p><i>Significant predictive factors for disability:</i></p> <ul style="list-style-type: none"> ✓ Female sex (OR for CD: 2.03, 95% CI 1.53-2.69; OR for UC 1.76, 95% CI 1.23-2.53); ✓ Age >40 y at diagnosis for CD (OR 3.69, 95% CI: 1.83-7.42); > 55 y for UC (OR 2.93, 95% CI 1.68-5.14); ✓ Disease duration > 15 years (only CD: OR 1.67, 95% CI 1.15-2.43); ✓ Lower education level (OR for CD: 2.02, 95% CI 1.55-2.64; OR for UC: 2.59, 95% CI 1.81-3.70); ✓ Smoking (Only CD: OR 1.45, 95% CI 1.09-1.92); ✓ Surgical interventions (Only CD: OR 1.48, 95% CI 1.10-2.00); ✓ Use of anti-TNFα (Only CD: OR 1.86, 95% CI 1.43-2.43); Immunomodulator use (Only UC: OR 1.58, 95% CI 1.09-2.28); ✓ Extra-intestinal manifestations (OR for CD: 1.36, 95%CI 1.05-1.77; OR for UC: 2.13, 95% CI 1.47-3.09). 	Very Good	Spekhorst et al ⁴⁸

Table I. (Continued). Summary of the studies addressing predictive factors for work disability in IBD affected patients.

Study location (period of investigation)	Study design	Population	Disability rate	Predictive Factors of work disability	Quality Rating According to NOS	Ref.
Brazil (2010- 2014)	Cross-sectional study	Records of disease-aids and pensions of disability due to IBD (No. 15277)	<i>Temporary leaves:</i> a greater number of work losses due to UC than to CD. <i>Disability pensions:</i> rate consistently increased in CD compared to UC.	The female gender predominates in both temporary and permanent disability.	N/A	de SB Fróes et al ⁴⁴
Sweden (2006-2014)	Cohort study	CD population No. 20638 (female No. 10685; median age: 27 y, range: 20-38). Control population No. 102038 (female No. 52857; median age: 27 y, range: 20-38).	<i>Disability pension rate:</i> the disability pension rate in CD patients vs. the general population was 2.34 (95% CI 2.25-2.43). More women received disability pension (20% of patients and 8.2% of controls, risk ratio 2.43 [95% CI 2.32-2.55]) than men (10% vs. 4.8%, risk ratio 2.17 [95% CI 2.02-2.33]). Disability pension was less common in ages 19-39 (4.3% vs. 2.4%, risk ratio 1.77 [95% CI 1.57-2.00]), than in ages 40-59 years (18% vs. 7.2%, risk ratio 2.57 [95% CI 2.44-2.70]), and ages 60-64 years (35% vs. 16%, risk ratio 2.23 [95% CI 2.09-2.38]).	<i>Significant predictive factors for disability in CD patients:</i> ✓ Structuring (RR 1.31, 95% CI 1.21-1.41); penetrating (RR 1.45, 95% CI 1.33-1.58); perianal disease (RR 1.37, 95% CI 1.27-1.47) ✓ Extraintestinal manifestations (RR 1.78, 95% CI 1.67-1.91) ✓ Use of biologics (RR 1.65, 95% CI 1.54-1.78) ✓ Use of immunomodulators (RR 1.24, 95% CI 1.16-1.31) ✓ Bowel surgery (RR 1.35, 95% CI 1.26-1.43); Perianal surgery (RR 1.38, 95% CI 1.26-1.51) ✓ Disease duration (>10 years) (RR 1.24, 95% CI 1.16-1.33)	Very Good	Everhov et al ⁴⁷
Canada (September 2015- March 2016)	Cross-sectional study	Total IBD population No. 207 (female No. 119; median age: 39 y; range: 27-53 y); UC patients No. 63; CD patients No. 144.	<i>Moderate to severe disability:</i> reported by 30.5% of patients. <i>Severity of disability assessed through the IBD disability index (IBDDI):</i> No disability: 40.3%; Mild disability: 29.1%; Moderate disability: 15.5%; Severe disability: 15%.	<i>Significant predictive factors for disability:</i> ✓ Disease activity: OR 45.7 (4.30-486.62) Self-efficacy was significantly less associated with disability: OR 0.7 (0.57-0.85)	Satisfactory	Chao et al ⁴⁶

CD, Chron's Disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HR, hazard ratio; OR, odds ratio; IBD, inflammatory bowel disease; RR, relative ratio; SIBDQ, short inflammatory bowel disease questionnaire; UC, ulcerative colitis;

IBD Related Factors

Type of IBD. As mentioned above, IBD primarily includes CD and UC. Although similar, such pathologies present some differences in terms of pathological and clinical features. In assessing whether one of the two diseases was most likely related to work disability, several studies^{22,23,28,42,43} pointed out that CD may represent a more reliable predictive factor, compared to UC. In particular, a first study²³ demonstrated that, among a population of Dutch patients with IBD, the risk for chronic work disability, was significantly increased in CD compared to UC patients. This work explored official disability under the social security system given to patients who have an objective medical restriction in earning their gross income. These results were confirmed by Bernklev et al²² who reported that the disability pension rate in 495 IBD patients, 5 years after the initial diagnosis, was comparable (8.5%) to that found in the general background Norwegian population (8.8%). However, the combination of diagnosis and gender, could point out that CD women, but not men, had a 3 to 4 times higher disability pension rate compared to UC patients. A significant increase in the full disability pension rate was found in CD compared to UC patients in the study performed by Mandel et al²⁹, and also a significantly higher work disability rate, assessed by the Work and Social Adjustment Scale, was reported by Israeli et al¹⁹ in CD patients compared to UC. Overall, this could reflect the fact that CD patients often have a more serious disease course than UC patients and thus have greater difficulties with regard to work, education, and participating in social life²².

In line with these previous results, Van der Valk et al²⁸ found that a significantly higher rate of CD patients (18.3%) were fully disabled compared to UC patients (9.5%). These subjects, according to the definition adopted by the Dutch social security system, were those declared to be >80% disabled and entitled to receive an income replacing disability benefit. When the partial disability, intended as >35%, but not fully and permanently, was assessed, a significantly lower percentage was reported in UC (5.4%) compared to CD patients (8.8%).

Temporary and permanent disability were investigated in a large study carried out on 1187 patients³⁴. Temporary disability was intended as a dichotomous end point assessed as have being absent from work during the follow-up period (1 year). Permanent work disability was defined as incident cases during follow-up, reaching a re-

ported disability degree of at least 70% as a result of IBD. The authors found that the number of patients with at least 1 absence was higher in the UC group at enrolment, but this difference decreased at the time of follow-up. In contrast, patients with CD were more likely to be permanently disabled than patients with UC, although these figures converged at follow-up as well. Comparably, a Brazilian study⁴⁴, carried out on records of disease-aids and pensions of disability between 2010 and 2014, obtained from the computerized social security system, demonstrated that temporary and permanent disability occurred more frequently in UC and CD, respectively.

Additional conflicting evidence on the predictive role of IBD type on work disability have been reported. Ramos et al⁴³ demonstrated that, among a population of 293 IBD patients, the disability pension rate was similar between UC (4.6%) and CD patients (3.5%). However, this study investigated also the rate of moderate to severe disability not qualifying for pensions, reporting that 93 (31.8%) patients had an officially recognized degree of disability which ranged from 24% to 100%. Interestingly, although the univariate analysis found that the rate and severity of such disability were significantly higher in CD compared to UC patients, the multivariate analysis did not confirm such result. In Høivik et al²⁷, disability pension rate was not significantly different between UC and CD patients, although significantly more CD patients were on rehabilitation programs when compared to those affected by UC. Vester-Andersen et al⁴⁵, reported similar disability pension granting in UC (5.8%) and CD patients (5.8%), also in comparison to the background population (3.1%).

Disease course. The clinical course of IBD is characterized by remissions and relapses of various intensity, often requiring hospitalizations and surgery, necessitating work absences and resulting in work disability¹. A more serious course of disease (continuous disease activity vs. only one lifetime episode of disease or recurring episodes of disease) was reported as a determinant of chronic work disability²³. Siebert et al³⁴, through a longitudinal multivariate analysis comparing enrolment data with those at 1-year follow-up, could demonstrate that temporary and permanent work disabilities were significantly predicted by the CD and UC active status indicated by higher severity index scores. In line with these findings, Ramos et al⁴³ showed that CD and UC activity was a signifi-

cant predictive factor for disability pension, as well as for any grade of disability, although this latter finding was not more confirmed at a multivariate analysis. Van der Valk et al²⁸ demonstrated that self-reported disease activity in CD patients, was significantly associated with work disability. In a more recent study, Chao et al⁴⁶ confirmed the CD and UC clinical disease activity to be a significant negative predictive factor for work disability and productivity loss.

Interestingly, in the attempt to define whether clinical factors in early disease course could predict work disability after ten years of disease, Høivik et al²⁷ demonstrated that increased levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) during the first year of the disease were significantly associated with an increased risk for long-term work disability in UC patients. In this study, work disability was defined in all patients applied for, or granted with rehabilitation benefits or disability pension due to IBD at the 10-year follow-up time point. Additionally, variables reflecting disease severity, i.e., number of visits to the specialist, taking drugs for IBD, were reported to be associated with a more than doubled rate of reduced work capacity and disability pension in CD patients compared to the background population⁴². The logistic regression analysis found that the disease course in the preceding year was significantly associated to disability pension. In Israeli et al¹⁹, long term disease activity was significantly associated with work disability in CD, but not in UC. As regards the role of the number of relapses in predicting work disability, more than two relapses occurred in the first year after diagnosis was significantly associated with work disability ten years later in UC patients as reported by Høivik et al²⁷. However, this result could not be observed in CD^{27,29}.

Concerning pattern of disease, Van der Valk et al²⁸ reported that penetrating course was significantly associated with work disability in CD. Ramos et al⁴³ reported that perianal disease, fecal incontinence and the number of diagnostic tests and medical visits performed in the previous year were predictors of disability. In a more recent study, Everhov et al⁴⁷ showed that CD patients with a structuring, penetrating, or perianal disease were associated with an increased risk of receiving disability pension. Conversely, in Ananthakrishnan et al¹⁸ luminal, fistulising, or structuring CD patterns were not associated with being disabled as also confirmed by other studies^{29,40,45}. Moreover, the disease phenotype at di-

agnosis did not predict work disability in either UC or CD patients²⁷.

Age at diagnosis and duration of disease. Although CD and UC can occur at any age, people are more frequently diagnosed between the ages of 20-30 years. As the world's population is ageing, it is not unexpected that the number of patients receiving a diagnosis of IBD later in life will increase. Concerning the impact of the age at the diagnosis on CD work disability, Vester-Andersen et al⁴⁵ found that patients older than 55 years of age at diagnosis (as compared with CD aged 18-55) were at increased risk of work disability. In line with these findings, an age > 40 years at the diagnosis was reported to be a risk factors for the long-term full work disability of CD patients in Sperkhost et al⁴⁸. Age at the diagnosis was not associated with a higher disability rate in CD patients in the study by Ananthakrishnan et al²⁰. As regards UC patients, Høivik et al²⁷ demonstrated that among variables associated with an increased risk for long term disability, an age older than 40 years could be included as a predictive factor.

About disease duration, defined as the time in years from diagnosis to the enrolment, Mandel et al²⁹ reported that disease duration for CD as a factor associated with an increased risk for disability pension, as was also detected by Israeli et al¹⁹. Conversely, Siebert et al³⁴ reported a worsened disability outcome in patients with short CD duration, while patients with UC were more likely to be disabled when having longer disease duration. These latter results are in line with those obtained by Ramos et al⁴³ demonstrating that time from IBD diagnosis was one of the most powerful predictive factor for disability as its degree clearly increased in patients with long-standing disease. A disease course >15 years was a significant predictor for a long-term full work disability in CD⁴⁸. Everhov et al⁴⁷ showed that CD patients with more than 10 years of disease had an increased relative risk of disability pension compared to those with shorter disease duration. No significant association was determined between duration of the disease and work disability in the study by Ananthakrishnan et al²⁰ and Van der Valk et al²⁸, although a non-significant trend towards a higher disability rate in subjects with disease duration greater than 5 years, could be observed.

Comorbidity. Early identification of comorbid conditions is crucial when managing patients with IBD because they can influence disease prognosis, pharmacological therapeutic approach, as well as quality of life, and work disability. A

significant association between the presence of concomitant extraintestinal manifestations and work disability was reported, although specific diseases were not deeper detailed⁴⁸. Extraintestinal rheumatic manifestations, i.e., arthritis/arthralgia, were reported as a predictive factor for disability pension in IBD²³ and CD patients^{29,47}. Van der Valk et al²⁸ showed that presence of joint manifestations, chronic back pain, and depression as IBD comorbidities were significant risk factors for work disability in both CD and UC. However, in Stjernman et al⁴² extraintestinal manifestations were not demonstrated to contribute to work disability in CD patients.

Demographic and Social Factors

Age. Data on work disability with respect to age showed conflicting results. Bernklev et al²² found an age dependent increase in disability pension rate in Norwegian CD patients, with the most pronounced rise, compared with the general population, detected between 30 and 50 years. In line with these previous findings, in some studies, older age was demonstrated as a predictive factor for patients applying for disability pension^{28,34,42,43,45,48}. The proportion of subjects receiving a disability pension was significantly higher in IBD patients older than 55 years⁴⁵, as well as in CD patients with > 40 years compared to 19-39 years old subjects⁴⁷. In a multivariate model, Spekhorst et al⁴⁸ demonstrated that in a population of Dutch IBD patients, an age >55 years was associated with a long-term full work disability in both CD and UC, a result that could be confirmed by Van der Valk et al²⁸ only in UC patients.

However, other investigations failed to confirm such findings. The rates of disability pension for UC patients, resulted comparable or lower to that of the general population in subjects <39 years and >39 years, respectively²². Høivik et al²⁷ reported that in an age stratified analysis, the relative risk for receiving a disability pension was highest in the youngest patient group in both CD and UC. Comparable results were obtained by Mandel et al²⁹ in which CD patients ≤ 45 years showed a significantly increased risk for a full disability pension compared to the gender and age-matched background population, while older patients (> 46 years) did not show any significant increased risk.

Sex. Women with IBD have been reported to receive more disability pension than men^{22,23,27,28,42,47}. In a clinical multinational trial on highly selected moderately to severely ill patients

with CD, female sex was associated with a greater risk of unemployment, and a tendency to a greater rate of disability pension²⁴. Female gender was reported as a significant predictor for temporary work disability only in CD patients³⁴. The impact of female gender concurs with findings from other studies^{22,27}. Bernklev et al²² found that women with CD had a 3 to 4 times higher disability rate (22.5%), assessed as disability pension, than men with CD, as well as UC patients of both genders. In line with these findings, Høivik et al²⁷ observed that women with CD had the highest risk for receiving a disability pension among all IBD patients enrolled, while no comparable gender related difference could be found for UC. Everhov et al⁴⁷ reported that the disability rate was significantly increased in women with CD compared to men. The same results were obtained by Stjernman et al⁴² in CD patients, in which a significant association between the female gender and work disability was assessed. Van der Valk et al²⁸ indicated that females with CD, but not UC, were prone to disability as well. Spekhorst et al⁴⁸ reported that female sex was significantly associated with CD and UC fully work disability intended as >80% work disability for >2 years.

No association between gender and disability pension or any degree of disability was reported by Ramos et al⁴³, Boonen et al²³, Ananthakrishnan et al²⁰, and Vester-Andersen et al⁴⁵, who found a sex-neutral three-fold rise in age-adjusted disability pension rate in CD, no gender related increase in disability rate, as well as a significantly increased risk of work disability pension in male IBD patients, respectively.

Education. Boonen et al²³ showed that the educational level was a determinant for chronic work disability, with lower and middle educational levels having a greater risk for work disability compared to patients with a higher educational level. Comparably, two groups of researchers^{28,46} demonstrated a significant association between a lower educational level and a full work disability in both CD and UC patients. On the other hand, in Everhov et al⁴⁷ the highest relative risk of receiving disability pension compared to the general population was found in those with >12 years of education followed by those with 10-12 years and ≤9 years. However, other investigations failed to determine an association between education level and work disability^{42,45}.

Treatment-Related Modifiers

Medication use: IBD treatment may include use of anti-inflammatory, immunomodulatory,

and biologic drugs. Høivik et al²⁷ reported that steroid treatment at the 1-year follow-up predicted work disability after 10 years disease in both CD and UC. Conversely, in patients with CD the use of immunosuppressants and not using steroids also worsened the outcome. Van der Valk et al²⁸ showed that previous use of corticosteroids was an independent predictor for work disability in UC, while medication use in CD patients was not a significant predictive factor. Exposure to steroids, or the need for immunosuppressants or biological therapies were not associated with increased risk for disability pension in CD²⁹.

Conversely, Ramos et al⁴³ reported the need for anti-TNF treatment were predictors of disability, intended both as disability pension and any degree of disability. In particular, in their study, the need for biological drugs emerged as the major predictor of qualifying for a disability pension. A significantly higher risk of work disability was reported by Spekhorst et al⁴⁸ in CD patients with anti-TNF treatment, as well as in UC patients reporting immunomodulator employment. Everhov et al⁴⁷ found that patients with ever-use of biologics or immunomodulators had a significantly higher risk of disability pension.

Surgery. Concerning the role of surgery in affecting work disability, Feagan et al²⁴ found that prior bowel resection in CD predicted a higher likelihood of receiving disability compensation. In line with this finding, Ananthkrishnan et al²⁰ could demonstrate that CD patients who had two or more medical hospitalizations or gastrointestinal surgeries for their CD had a significantly higher risk to be on Social Security disability. Comparably, Everhov et al⁴⁷ reported that CD patients undergone bowel or perianal surgery had a significantly higher risk to receive disability pension. Van der Valk et al²⁸ could observe that abdominal surgery, ileostomy or colostomy were significantly associated with work disability in CD. More recently, Spekhorst et al⁴⁸ reported that surgical interventions were associated with an increased risk for work disability in CD patients. Number of surgeries and number of diagnostic procedures performed during the previous year resulted as independent predictive variables for having any degree of disability in Ramos et al⁴³. Concerning UC, abdominal surgery was found to be a significant, independent, predictor of work disability²⁸. These findings are in line with those obtained by Høivik et al²⁷ that demonstrated that early colectomy, before the 1-year follow-up, predicted work disability in UC patients. Conversely, Israeli et al¹⁹ failed to find an association between

IBD related surgeries and hospitalizations and disability rates assessed through the Work and Social Adjustment Scale, as also reported in the study by Vester-Andersen et al⁴⁵.

Discussion

This review represents the first attempt to provide a comprehensive overview on the factors that may function as predictors for the development of work disability in IBD patients. Several predictors were suggested by different studies, although with not always homogeneous results. The importance to define such factors may rely on their possible use as an early warning system, enabling physicians and patients to better predict the course of their diseases and ideally prevent adverse outcomes through suitable interventions³⁴.

Having CD has been reported as a possible predictive factor for work disability in different investigations^{19,22,23,28,29,42}. This result may be explained by the natural history of CD, that generally has a more serious course and complications than UC²². However, when temporary and permanent disability were assessed, the first one was more frequently reported in UC than CD patients, who had a significantly greater risk to be permanently disabled^{34,44}. This latter finding may reflect the more permanent nature of the structural damage caused by CD compared to UC. However, the limited number of studies addressing this issue and the possible relationship between IBD and any degree of disability, does not allow to extrapolate definite conclusions and requires deeper research.

In addition to CD, additional major groups of parameters have been reported to modulate disability in IBD, such as factors related to the disease course, including disease activity and severity as well as the need for specific medical or surgical treatment. Concerning disease severity, one might predict the patients with the most severe symptoms and refractory disease may have greater problems in performing their work. In this case, one would hypothesize that the positive and negative predictors for work disability are the same as the predictors for disease outcome. Indeed, work disability in IBD was associated with an active status of the disease^{23,28,43,45}. However no conclusive evidence has been obtained concerning the role of the multiple variables resembling disease activity or severity, i.e., specific symptoms⁴³, frequent relapses^{27,29}, pattern of disease^{27-29,40,43,45,47}, number of diagnostic tests or medical visits previously performed⁴³

in predicting work disability, therefore requiring additional investigation. Moreover, the association between alterations in inflammatory biomarkers and disability rate should be clarified in order to define suitable biochemical parameters that may objectively predict work disability in the follow-up of patients²⁷.

As regards medication use, conflicting pieces of evidence²⁷⁻²⁹ are available on the predictive role of steroid therapies in work disability. Although conclusive evidence cannot be extrapolated, it cannot be excluded that steroid therapy may function as a marker of severe/continuous disease that may, in turn, be potentially responsible for work disability. In this perspective, the severity of the disease may also influence the use of biologics, explaining the association between such type of treatment and an increased work disability rate^{43,47,48}. Any beneficial effects of biologics use may be confounded by the treatment indication, leading to noncausal effect estimates³⁴. In line with this consideration, it may be expected that surgery would reduce the risk for work disability. However, the lack of this finding^{20,24,27,28,43,47,48} may be dependent by the fact that the rate of hospitalizations and the number of surgical treatments are indirect markers of more severe diseases and may predict an aggressive IBD course. Moreover, work disability might be the result of the surgical disabling sequelae, as well as postoperative complications, i.e. fecal incontinence, having an ostomy as well as pouchitis⁴³.

Regarding the demographic and sociological factors, the effect of age on work disability is unclear^{22,27,29,34,42,43,45,48}. Conversely, the female gender has been reported as a possible risk factor for work disability in IBD patients^{22-24,27,28,34,42,47,48}, although with some conflicting evidence^{20,23,43,45}. Some specific gender-related consequences of perianal or fistulizing disease, the possible greater impact of extra-intestinal manifestations in women, as well as sex inequalities in society and family life, leading to greater demands on expectations of daily function for females should be deeply investigated as potential determinants of gender-related impact on work disability^{21,42}. Additionally, it should be considered that males may be more negatively affected by being outside the workforce than females^{27,49}. Consequently, males might postpone an exit from the workforce, which could, in part, explain the above mentioned findings. The possible predictive role of education on work disability is worthy of further investigations^{23,42,45,47}. However, a possible link relies

on the fact that, in general, the level of education is strictly connected with socioeconomic status, thus suggesting the association between this one and disability rate.

Although some interesting predictors could be pointed out from our revision, some critical aspects need to be considered for a correct interpretation of the results and a suitable planning of future studies. The first one relies on the fact that most of the revised investigations addressed work disability as granting a disability pension. Although in some cases such information was retrieved from social security system registries, in several studies available data were gathered from patient reports that may contain information bias³⁴. Ideally, future investigation should overcome such possible recall bias through their validation *via* other sources, such as physician questionnaires, work or public tax records.

Moreover, currently available studies may have underestimated the real degree of disability by not including in the disabled group patients with severe disturbances, i.e., having an ostomy or fecal incontinence, but who had not requested either a disability pension or a formal evaluation for disability. Moreover, the concession of disability pensions may suffer from geographical variability, suggesting a degree of inequity in the system and preventing a suitable comparison of data.

As an overall result, the award of disability pensions may not reflect exactly the true degree of disability of IBD patients. In this perspective, in fact, only a couple of studies reported data on the rates of moderate to severe disability in IBD patients not qualifying for pensions⁴³ or on temporary or permanent disability³⁴. Future longitudinal investigation in this regard, should be focused not only on disability pension as a dichotomous variable, but also on additional parameters able to provide a more complete figure of the “work disability” scenarios, better resembling the frequency and severity of the phenomenon and of its trend with time after diagnosis.

The assessment of work disability/disability pension rate in IBD patients covers only the terminal part of the “disease continuum” impact of CD and UC on work ability of patients. It does not cover ability impairments and productivity losses in people showing up at work but having reduced efficiency as a result of IBD morbidity. Therefore, further research should also consider this kind of impact on the occupational life of IBD patients, assessing additional aspects, i.e., absenteeism, presenteeism, activity impairments

and productivity loss, therefore supporting a better understanding of the difficulties in performing their works.

In this regard, as work disability may be related to physical and psychological requirements of particular occupations, that are, the job profiles and occupational risks experienced, attention should be paid also in understanding which kind of occupational realities may have a greater impact on the work disability, as well as on the work capacity. This may be helpful to provide guidance to achieve an adequate risk assessment procedure in occupational setting and to adopt suitable preventive and protective policies. These may include also administrative interventions promoting more flexible and tailored working conditions, as well as workplace accommodations, aimed to avoid severe consequences on the health of IBD workers.

Moreover, social background and personal attitudes and beliefs that may strongly modulate the degree of disability/impaired capacity to work induced by a given physical alteration should be taking into suitable account. Importantly, in the perspective of a possible bidirectional relationship between work impairments and the activity status of disease and its severity, as suggested by the reported findings, a more comprehensive approach for an effective management of IBD patients should verify not only whether clinical parameters may be predictive for work disability, but also whether early signs of occupational impairments may, in turn, predict a worst evolution of the disease.

Conclusions

The findings emerged from our review support the need for further investigation exploring the impact that IBD may have on work ability of affected patients overcoming the more limited concept of “work disability”. In this perspective, taking into account that work may be a key element in achieving a good quality of life, the impairments in work ability due to IBD should be considered an integral part of the patient disease evaluation and management. This may require a multidisciplinary approach based on the concerted efforts of general practitioners, gastroenterologists, occupational physicians and psychologists taking care for IBD workers aimed to control their clinical symptoms while improving their psychosocial and professional well-being.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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