High Disease Burden Drives Indirect Costs in Employed Inflammatory Bowel Disease Patients: The WORK-IBD Study

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Background: Work productivity (WP) loss includes absence from work (absenteeism) and productivity loss while working (presenteeism), which leads to high indirect costs in inflammatory bowel disease (IBD). Prior health economic analyses predominantly focused on absenteeism. Here we focus on presenteeism and assess predictors of WP loss, fatigue, and reduced health-related quality of life (HRQL).

Methods: Employed IBD patients completed the following surveys: Work Productivity and Activity Impairment, Multidimensional Fatigue Inventory, and Short Inflammatory Bowel Disease Questionnaire. Predictors were assessed using uni- and multivariable regression analyses. Annual costs were calculated using percentages of WP loss, hourly wages, and contract hours.

Results: Out of 1590 invited patients, 768 (48%) responded and 510 (32%) were included. Absenteeism, presenteeism, and overall WP loss were reported by 94 (18%), 257 (50%), and 269 (53%) patients, respectively, resulting in mean (SD) annual costs of €1738 (5505), €5478 (8629), and €6597 (9987), respectively. Disease activity and active perianal disease were predictors of WP loss (odds ratio [OR] = 6.6; 95% confidence interval [CI], 3.6-12.1); OR = 3.7; 95% CI, 1.5-8.7). Disease activity and arthralgia were associated with fatigue (OR = 3.6; 95% CI, 1.9-6.8; OR = 1.8; 95% CI, 1.0-3.3)) and reduced HRQL (OR = 10.3; 95% CI, 5.9-17.9; OR = 2.3; 95 % CI, 1.4-3.8). Fatigue was the main reason for absenteeism (56%) and presenteeism (70%). Fatigue and reduced HRQL led to increased costs compared with absence of fatigue and normal HRQL (mean difference = €6630; 95% CI, €4977–€8283, $P < 0.01$; mean difference = €9575; 95% CI, €7767–€11,384, $P < 0.01$).

Conclusions: Disease activity and disease burden lead to WP loss in approximately half of the employed IBD population, driving indirect costs. Fatigue is the most important reason for WP loss.

Key Words: inflammatory bowel disease, health economics, work productivity

INTRODUCTION

Inflammatory bowel disease (IBD) significantly impacts daily life.[1] Physical and emotional problems that are associated with IBD include diarrhea, abdominal pain, fatigue, depression, and anxiety. Crohn's disease (CD) and ulcerative colitis (UC), collectively known as IBD, are mainly diagnosed between ages 15 and 30 years, the same period in which young individuals often start their careers and families.

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Several studies have shown that IBD is associated with lower employment rates and higher percentages of work disability compared with the healthy population.[2-6] Previously described predictors of unemployment and work disability include early age of disease onset, female gender, disease duration, disease activity, reduced health-related quality of life (HRQL), fatigue, and extraintestinal manifestations.[2, 5, 7, 8] A large proportion of working IBD patients experience difficulties at work, including concentration problems and reduced work productivity (WP).[9]

Because it is known that medication adherence and adequate disease control lead to less disability and improved quality of life in IBD,[10, 11] it is hypothesized that the disease burden can vary considerably between patients who receive different maintenance treatment regimens. However, the use of specific therapeutic agents in patients with IBD can be a confounding factor because it may indirectly reflect disease severity. This phenomenon may explain, at least partly, the outcomes of a French nationwide survey that showed that anti-tumor necrosis factor (TNF) use was associated with poor quality of life, severe fatigue, and WP loss.[12]

Altogether, unemployment and work disability in IBD patients contribute to health care costs. Health care costs can be measured in terms of direct and indirect costs. So far, the majority of health economic analyses in the IBD field have focused on so-called direct health care costs (including treatment, hospitalization, and surgery-related costs) and concluded that direct costs are mainly driven by drug costs.[13, 14] In contrast, only a few studies have investigated indirect costs (expenses incurred from WP loss) by measuring abcence from work (absenteeism).[15, 16] However, on-the-job productivity loss (presenteeism), caused by IBD-related problems, also represents a significant problem.[6] It has been shown that at least one-third of patients with IBD experience reduced productivity while working, indicating WP loss occurring without being absent from work.[17] Therefore, excluding presenteeism in economic evaluations leads to an underestimation of indirect costs related to IBD.

The aim of the present study was first to assess predictors of severe WP loss, fatigue, and reduced HRQL in employed IBD patients. Second, we aimed to estimate indirect costs incurred from both absenteeism and presenteeism. The ultimate goal was to identify potential targets that can be optimized to improve clinical outcomes in employed IBD patients with paid employment, resulting in reduced indirect costs.

METHODS

This cross-sectional study was conducted as part of the ongoing web-based WORK-IBD study. Patient-reported outcome data and perceived disease severity in patients with IBD were prospectively collected using online surveys at baseline and every 6 months during a 2-year follow-up period.

Study Population

Patients between ages 16 and 63 years, diagnosed with UC or CD by endoscopy and histopathology, and attending the outpatient clinic of 4 hospitals in the Amsterdam region (2 academic and 2 nonacademic hospitals) between May 1, 2017, and August 31, 2017, were invited to participate by letter. Patients who gave consent for participation and who were in paid labor were eligible for inclusion. Paid labor was defined as (1) working as an employee, (2) working as an independent entrepreneur, or (3) partially disabled and partially working (receiving a partial sickness benefit). Patients actively participating in a placebo-controlled trial (in which the investigational medicinal product was unknown) at the time of invitation and patients using experimental treatments (ie, not receiving standard care) were excluded. Patients with unspecified IBD were also excluded from participation.

Ethical Considerations

The Medical Ethics Review Committee of the Academic Medical Centre (Amsterdam, the Netherlands) granted a waiver for this study and confirmed that the Medical Research Involving Human Subjects Act did not apply to this study (W17_190).

Data Collection and Outcome Measurements

Eligible patients received an invitation to complete the online baseline questionnaire by use of the cloud-based Castor Electronic Data Capture platform, or a paper questionnaire was sent, according to patient preferences.[18] The baseline questionnaire included sociodemographic, work-related, and disease-related questions. Questionnaires included the Work Productivity and Activity Impairment (WPAI) questionnaire to measure absenteeism, presenteeism, and overall WP loss;[19] the Multidimensional Fatigue Inventory (MFI) to quantify fatigue;[20] and the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) to determine HRQL.[21] The patient-reported Simple Clinical Colitis Activity Index (p-SCCAI) for UC and patient-reported Harvey Bradshaw Index (p-HBI) for CD were used to determine clinical disease activity.[22, 23] The p-SCCAI and p-HBI were developed to measure patient-administered clinical disease activity and have shown moderate to substantial agreement with clinician-administered SCCAI and HBI scoring systems.[22, 23] Additional patient data, including laboratory and imaging outcomes and specific treatment information, were retrieved by chart review and also entered manually in the Castor Electronic Data Capture platform.

The WPAI measures time missed from work and work impairment because of IBD in the past week.[19] Absenteeism is the percentage of work hours missed because of IBD in the previous week (thereby also including the hours of partial sickness benefit because of IBD), presenteeism is defined as a score on a 0-10 (maximum impairment) scale, and overall WP loss

is calculated using the following calculation: (absenteeism +] (1 - absenteeism) × presenteeism]).[24] Severe absenteeism, presenteeism, and overall WP loss were defined as ≥50% work hours missed because of IBD, ≥50% productivity loss while working (score ≥ 5), and ≥50% overall WP loss, respectively. When patients reported absenteeism or presenteeism they had to report the main IBD-related reason(s) for their absenteeism or presenteeism.

The 20-item MFI (ranging from 20 to 100, with higher scores indicating more severe fatigue) can be divided into 5 subscores: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[20] Severe fatigue was defined as a general fatigue score above the 95th percentile of the general population corrected for age and gender.[25]

The SIBDQ comprises 10 questions, and the total score ranges from 10 (worst health) to 70 (best health).[21] Because no cutoff value is known in the literature to define reduced HRQL, we defined reduced HRQL as a total SIBDQ score <50. Clinical disease activity was defined as a p-SCCAI or p-HBI score >4.[22, 23, 26-28]

Patients were subdivided into different treatment classes based on the treatment they were using at the time of completing the questionnaire and according to prior medication use. Immunomodulator- and biologic-naïve patients were represented by patients who never used a biological or immunomodulator (thiopurine or methotrexate). The biologic-naïve patient group (without being immunomodulator-naïve) consisted of patients who had never used a biological and who used at least 1 immunomodulator (prior or active use). Patients in the "first-class biologic" group used or had used 1 class of biologics (anti-TNF drugs, vedolizumab, or ustekinumab). Patients who received multiple anti-TNF agents were included in the first-class biologic group. The second- and third-class biologic group included patients who used 2 or 3 classes of biologic agents.

Statistical Analysis

Categorical data are presented as frequencies and percentages, continuous data as mean with SD, or median with interquartile range (IQR) according to distribution. We used χ^2 tests or Fisher's exact tests to compare categorical variables. Independent-samples *t* tests were used to compare normally distributed variables and Mann-Whitney *U* tests were used for nonparametric data. Factors associated with severe WP loss, severe fatigue, and reduced HRQL were identified by logistic regression analyses. Factors with $P \leq 0.1$ in univariable analysis were entered into multivariable analysis using backward elimination (likelihood ratio) with stepwise selection. Outcomes were presented with the odds ratio (OR) and associated 95% confidence interval (CI). Correlations between patient-reported outcomes were measured using the Pearson correlation coefficient and Spearman correlation coefficient according to distribution. A strong (inverse) relationship was indicated for correlation coefficient values above 0.7 or below –0.7. Annual indirect costs were calculated with data extracted from Statline (Statistics Netherlands), including average hourly wage corrected for gender and assuming an average of 47.4 weeks worked annually (excluding holiday hours based on a full-time work week) and with data collected with the WPAI survey (percentage of WP loss and individual contract hours).[29, 30] Indirect costs were presented as mean with SD. Additionally, indirect costs were presented using median with IQR in tables. When comparing 2 groups a mean difference and 95% CI were shown. A P value <0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics version 25.

RESULTS

Baseline Characteristics

Of the 1590 patients with IBD who were invited, 768 (48%) responded (Fig. 1). Of these 768 patients, 86 (11%) declined participation and 119 (15%) were not eligible: 31 (26%) were on full occupational disability, 4 (3%) had taken early retirement, 12 (10%) were students without a job, and 72 (61%) were unemployed for other reasons. Baseline questionnaires were sent to 563 patients and were completed by 536 patients (95%). Another 26 patients were excluded from further analyses after completing the baseline questionnaires because of complete occupational disability (no paid labor), leaving 510 patients to be included in the final analyses. Out of these 510 patients, 299 (59%) were female and 268 (53%) were diagnosed with CD (Table 1). At the time that they completed the questionnaire, 110 patients (22%) were using mesalazine as monotherapy, 108 patients (21%) were on immunomodulators (ie, thiopurines [94%] or methotrexate [6%]) with or without concomitant mesalazine, 122 patients (24%) were on anti-TNF drugs (41 [34%] in combination with an immunomodulator), 26 patients (5%) used vedolizumab (4 in combination with a thiopurine and 1 on concomitant adalimumab), 12 patients (2%) used ustekinumab (1 combined with mercaptopurine), and 132 patients (26%) received no maintenance therapy at all. The last group consisted of 55 patients (42%) with a history of bowel surgery (partial small bowel or colonic resections). Out of the patients who used vedolizumab or ustekinumab, the majority used these biologics as a second- or third-class biologic treatment (81% and 100%, respectively). Patients in the third-class biologic group all had CD, were relatively younger, were diagnosed at a younger age, and had a shorter disease duration compared with the total study cohort (Table 1). The largest proportion of patients with signs of disease activity at the time of completing the questionnaire (clinical disease activity or elevated calprotectin or C-reactive protein levels) were in the third-class biologic group.

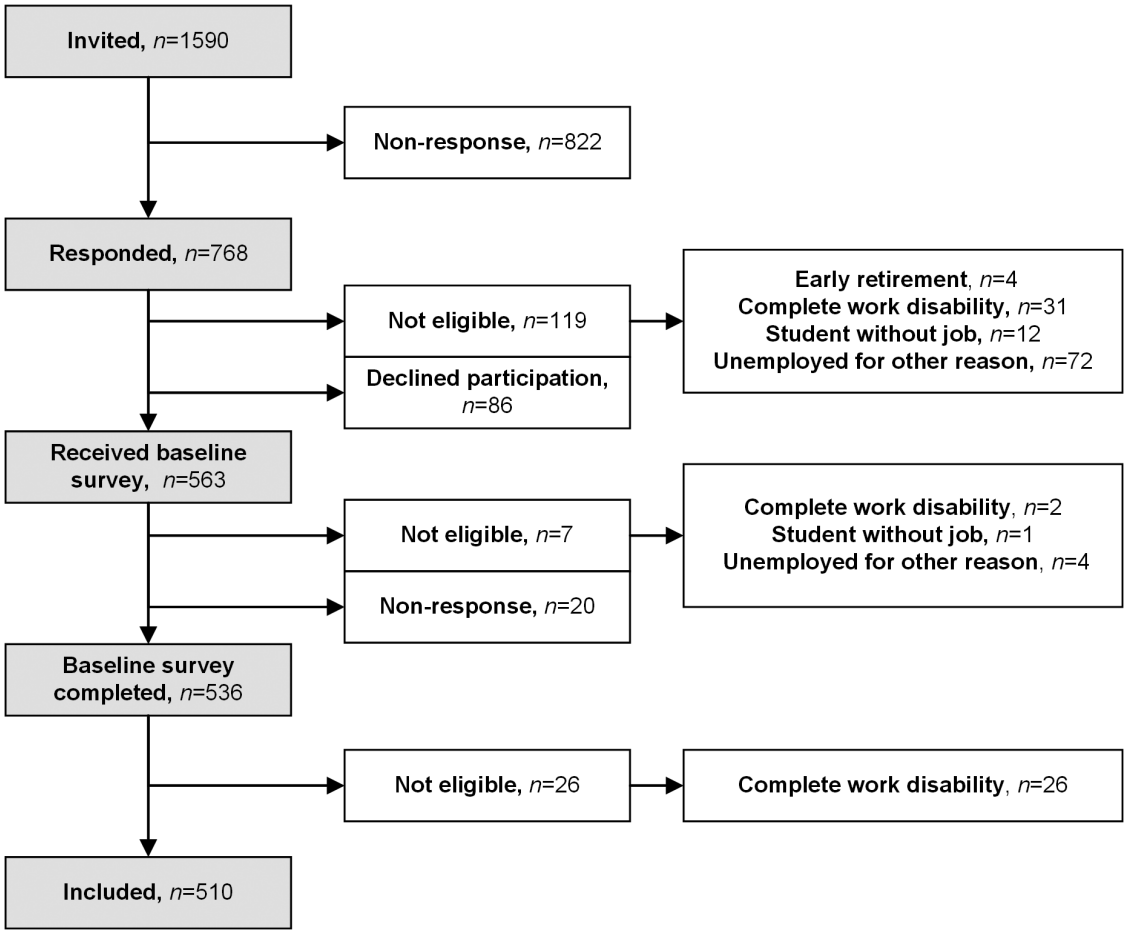

FIGURE 1. Flowchart of included and excluded patients.

Work Productivity Loss

Forty-two out of 510 (8%) patients reported being partially disabled (receiving a partial disability pension). Mean (SD) percentages of absenteeism, presenteeism, and overall WP loss were 5% (16), 17% (23), and 21% (27), respectively (Supplementary Table 1). Ninety-four out of 510 (18%) patients reported absenteeism, 257 (50%) reported presenteeism, and 269 (53%) reported any form of WP loss because of IBD-related problems in the past week. Severe absenteeism, presenteeism, and overall WP loss in the past week were reported by 20 (4%), 83 (16%), and 99 (19%) patients, respectively (Fig. 2). The highest and lowest percentages of patients with severe overall WP loss were found in the third-class biologic (50%) and immunomodulator- and biologic-naïve (8%) groups, respectively. A significantly higher proportion of CD patients reported severe WP loss compared with UC patients (27% vs 12%; $P < 0.001$).

Predictors of severe WP loss

Multivariable analysis in the total IBD cohort showed a significantly higher incidence of severe WP loss in patients with active perianal disease (OR = 3.4; 95% CI, 1.4-8.3) and in patients with clinical disease activity (OR = 6.3; 95% CI, 3.3-11.8) and an independent significant lower incidence in IBD patients who actively used 5-aminosalicylate (5-ASA) treatment (OR = 0.2; 95% CI, 0.0-0.9) (Table 2). In a multivariable subgroup analysis performed in patients with CD (excluding patients with UC), active perianal disease (OR = 3.3; 95% CI, 1.3-8.1) and clinical disease activity (OR = 7.2; 95% CI, 3.8-13.4) were found to be predictors of severe WP loss (Supplementary Table 2). No significant association was found between active 5-ASA use and a lower incidence of severe WP loss in the CD cohort (OR = 0.2; 95% CI, 0.1-1.1). Subgroup multivariable analysis in UC patients revealed that prior bowel surgery (OR = 5.7; 95% CI, 1.3-24.7), clinical disease activity (OR = 27.4; 95% CI, 9.3-80.9), and active anti-TNF use (OR = 9.0; 95% CI, 2.8-29.3) were associated with a higher incidence of severe WP loss (Supplementary Table 3).

Patient-reported reasons for WP loss

Fatigue was the most frequently self-reported reason for absenteeism (56%) and presenteeism (71%) (Fig. 3). In total, 13/94

TABLE 1. Baseline Characteristics

	Total	Immunomodulator- and Biologic-naïve	Biologic-naïve*	First-class Biologic†	Second-class Biologic‡	Third-class Biologic§
	n = 510	n = 119	n = 136	n = 208	n = 41	n = 6
Female, n (%)	299 (59)	73 (61)	77 (57)	124 (60)	21 (51)	4 (67)
Age, y, median (IQR)	45 (33–53)	47 (37–54)	45 (35–54)	43 (32–53)	39 (33–51)	29 (27–49)
BMI, median (IQR)	24 (22–27)	24 (22–27)	24 (22–27)	24 (21–27)	24 (22–27)	27 (20–30)
Dutch nationality, n (%)	423 (83)	95 (80)	119 (88)	168 (81)	36 (88)	5 (83)
Level of education, n (%)¶						
Low	87 (17)	15 (13)	30 (22)	34 (16)	8 (20)	0 (0)
Intermediate	122 (24)	28 (24)	34 (25)	49 (24)	10 (24)	1 (17)
High	301 (59)	76 (64)	72 (53)	125 (60)	23 (56)	5 (83)
Active smoking, n (%)	56 (11)	12 (10)	10 (12)	22 (11)	5 (12)	1 (17)
UC, n (%)	242 (48)	101 (85)	65 (48)	65 (35)	11 (27)	0 (0)
E1	39 (16)	31 (31)	4 (6)	3 (5)	0 (0)	0 (0)
E2	82 (34)	37 (37)	18 (27)	23 (35)	4 (36)	0 (0)
E3	113 (47)	29 (29)	41 (63)	37 (57)	6 (55)	0 (0)
CD, n (%)	268 (53)	18 (15)	71 (52)	143 (69)	30 (73)	6 (100)
A1	29 (11)	1 (6)	10 (14)	12 (8)	5 (17)	1 (17)
A2	198 (74)	11 (61)	47 (66)	112 (78)	23 (77)	5 (83)
A3	41 (15)	6 (33)	14 (20)	19 (13)	2 (7)	0 (0)
L1	83 (31)	10 (56)	19 (27)	48 (34)	6 (20)	0 (0)
L2	67 (25)	5 (28)	22 (31)	29 (19)	8 (27)	3 (50)
L3	113 (42)	1 (6)	29 (41)	65 (45)	15 (50)	3 (50)
L4	19 (7)	1 (6)	6 (8)	9 (6)	3 (10)	0 (0)
B1	161 (60)	12 (67)	46 (65)	83 (58)	15 (50)	5 (83)
B2	57 (21)	4 (22)	14 (20)	30 (21)	8 (27)	1 (17)
B3	46 (17)	0 (0)	10 (14)	29 (20)	7 (23)	0 (0)
Perianal‖	73 (27)	0 (0)	10 (14)	50 (35)	12 (40)	1 (17)
Disease duration, y, median (IQR)	11 (5–20)	8 (3–19)	11 (4–22)	12 (7–20)	14 (6–20)	9 (7–29)
Clinical disease activity, n (%)**	107 (21)	16 (13)	31 (23)	48 (23)	8 (20)	4 (67)
Active perianal disease, n (%)††	28 (10)	3 (16)	3 (4)	16 (11)	6 (19)	0 (0)
Active arthralgia, n (%)	163 (32)	36 (30)	46 (34)	63 (30)	17 (42)	1 (17)
CRP >5 mg/L, n (%)‡‡	81 (16)	11 (9)	17 (13)	36 (17)	13 (32)	4 (67)
Calprotectin ≥150 mg/kg, n (%)‡‡	82 (16)	12 (10)	18	37 (18)	13 (32)	2 (33)
Treatment in academic hospital, n (%)	308 (60)	36 (30)	80 (59)	154 (74)	34 (83)	4 (67)
Prior bowel resection, n (%)	131 (26)	8 (7)	30 (22)	71 (34)	20 (49)	2 (33)
Stoma, n (%)	28 (6)	1 (1)	3 (2)	15 (7)	8 (20)	1 (17)
IPAA, n (%)	14 (3)	1 (1)	1 (1)	9 (4)	3 (7)	0 (0)
Prior treatment, n (%)						
Anti-TNF	164 (32)	0 (0)	0 (0)	118 (57)	40 (98)	6 (100)
Vedolizumab	16 (3)	0 (0)	0 (0)	1 (0)	11 (27)	4 (67)
Ustekinumab	5 (1)	0 (0)	0 (0)	0 (0)	2 (5)	3 (50)
Current treatment, n (%)						
Topical therapy	61 (12)	34 (29)	13 (10)	14 (12)	0 (0)	0 (0)
Corticosteroid	28 (6)	5 (4)	8 (6)	9 (4)	6 (15)	0 (0)
5-ASA	184 (36)	73 (61)	56 (41)	48 (23)	7 (17)	0 (0)
Mercaptopurine	55 (11)	0 (0)	28 (21)	24 (12)	3 (7)	0 (0)
Azathioprine	58 (11)	0 (0)	34 (25)	21 (10)	3 (7)	0 (0)
Thioguanine	28 (6)	0 (0)	11 (8)	16 (8)	1 (2)	0 (0)
Methotrexate	13 (3)	0 (0)	3 (2)	8 (4)	2 (5)	0 (0)

TABLE 1. Continued

	Total	Immunomodulator- and Biologic-naïve	Biologic-naïve*	First-class Biologic†	Second-class Biologic‡	Third-class Biologic§
	n = 510	n = 119	n = 136	n = 208	n = 41	n = 6
Infliximab	65 (13)	0 (0)	0 (0)	63 (30)	2 (5)	0 (0)
Adalimumab	55 (11)	0 (0)	0 (0)	53 (25)	2 (5)	0 (0)
Golimumab	3 (1)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)
Vedolizumab	26 (5)	0 (0)	0 (0)	5 (2)	19 (46)	2 (33)
Ustekinumab	12 (2)	0 (0)	0 (0)	0 (0)	9 (22)	3 (50)
Contract hours, n (%)						
<12	17 (3)	1 (1)	5 (4)	8 (4)	3 (7)	0
12–35	249 (49)	56 (47)	63 (46)	103 (50)	24 (59)	3 (50)
≥36	242 (47)	62 (52)	68 (50)	95 (46)	14 (34)	3 (50)
Self-employed, n (%)	85 (17)	27 (23)	17 (13)	29 (14)	11 (27)	1 (17)
Breadwinner position, n (%)	270 (53)	59 (50)	79 (58)	109 (52)	20 (49)	3 (50)
Blue-collar work, n (%)	25 (5)	6 (5)	7 (5)	8 (4)	4 (10)	0 (0)

*Biologic-naïve patients who ever used thiopurines or methotrexate.
†Active or prior treatment with first-class biologic agent (anti-TNF, vedolizumab, or ustekinumab) without prior use of a biologic agent "out of class."
‡Active or prior treatment with second-class biologic agent (anti-TNF, vedolizumab, or ustekinumab) and thus prior use of 1 biologic agent out of class.
§Active or prior treatment with third-class biologic agent (anti-TNF, vedolizumab, or ustekinumab) with prior use of 2 biologic agents out of class.
¶Low level included elementary school, intermediate level included secondary (vocational) education, and high level included higher (vocational) education.
‖Documented history of perianal fistulizing disease.
**A p-SCCAI or p-HBI > 4.
††Only measured in patients with CD.
‡‡Measured ≤8 weeks before or after the survey completion date: in 119/510 and 242/510 patients, no CRP and calprotectin values were available.
A1 indicates disease diagnosed at age 16 years or younger; A2, diagnosed between ages 17 and 40 years; A3, diagnosed at older than 40 years; BMI, body mass index; CRP, C-reactive protein; E1, proctitis; E2, left-sided colitis; E3, pancolitis; IPAA, ileal pouch-anal anastomosis; IQR, interquartile range; L1, localized in ileum; L2, disease localization in colon; L3, disease localization in ileum and colon; L4, disease localization in upper gastrointestinal tract.

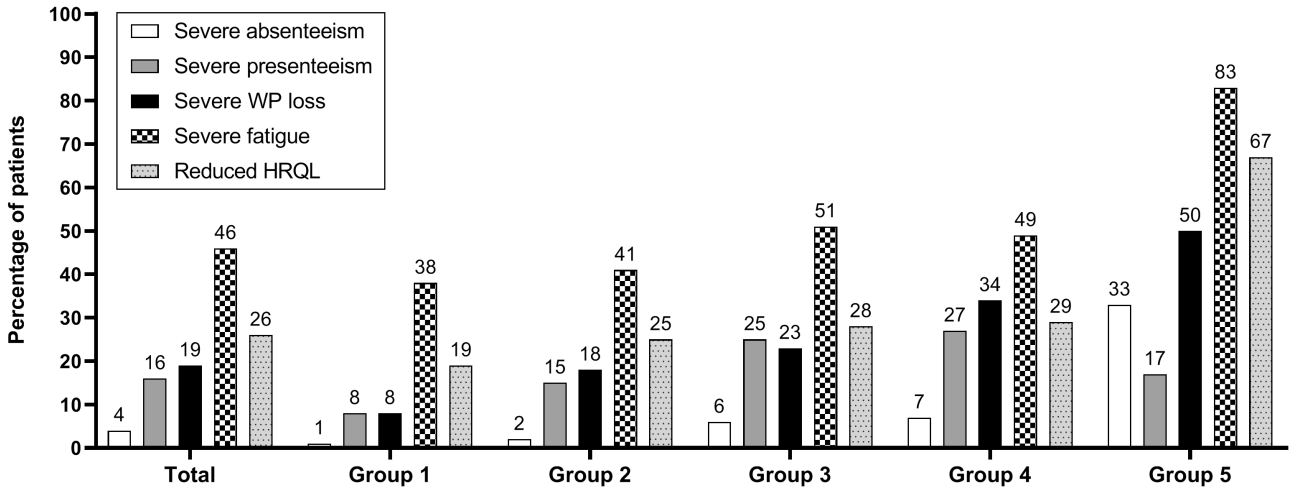

FIGURE 2. Percentage of patients with IBD with high disease burden. Group 1, immunomodulator- and biologic-naïve; Group 2, biologic-naïve; Group 3, first-class biologic; Group 4, second-class biologic; Group 5, third-class biologic.

(14%) of patients reporting absenteeism and 78/257 (30%) of patients reporting presenteeism noted fatigue as the only reason for absenteeism and presenteeism, without reporting another cause. Other frequently reported reasons for absenteeism included hospital visits (45%), abdominal pain (27%), frequent toilet visits interfering with work-related tasks (16%), adverse effects of IBD medication (15%), and problems traveling to work (12%). Abdominal pain (33%), bloating or abdominal discomfort (25%),

TABLE 2. Predictors of Severe Overall WP Loss in the Employed IBD Population

	Univariable Analyses			Multivariable Analysis		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Patient-related						
Female gender	0.99	0.63–1.55	0.966			
Age, y						
<30	2.17	1.25–3.76	0.006	ns		
30–50	Ref					
>50	0.96	0.57–1.62	0.876			
Active smoking	1.44	0.75–2.75	0.275			
BMI						
<18.5	3.11	1.06–9.12	0.039			
18.5–25.0	Ref					
>25.0	1.21	0.77–1.90	0.416			
Level of education*						
Low	1.04	0.53–2.02	0.917			
Intermediate	Ref					
High	0.80	0.48–1.36	0.410			
Work-related						
Self-employed	1.23	0.70–2.17	0.472			
Breadwinner position	0.66	0.42–1.02	0.063			
Blue-collar work†	0.55	0.16–1.89	0.343			
Contract hours per week						
0–12	1.53	0.52–4.54	0.441			
12–35	Ref					
≥36	0.75	0.78–1.18	0.214			
Disease-related						
CD (vs UC)	2.72	1.68–4.38	<0.01	ns		
Disease duration ≥10 years	0.76	0.49–1.18	0.219			
Bowel-related surgery‡	1.40	0.87–2.27	0.167			
Failed ≥1 biological	1.84	1.16–2.89	0.009	ns		
IPAA	1.68	0.51–5.46	0.392			
Stoma	1.13	0.45–2.87	0.794			
Active perianal disease	4.52	2.02–10.13	<0.001	3.38	1.37–8.34	0.008
Active arthralgia	2.56	1.63–4.01	<0.001	ns		
Clinical disease activity§	11.82	7.13–19.58	<0.001	6.29	3.34–11.83	<0.001
Treatment-related						
Active 5-ASA use	0.36	0.21–0.61	<0.001	0.19	0.04–0.92	0.038
Active immunomodulator use	1.01	0.63–1.63	0.976			
Active anti-TNF use	1.79	1.11–2.89	0.017	ns		
Active vedolizumab use	1.65	0.67–4.06	0.277			
Active ustekinumab use	6.13	1.90–19.76	0.002	ns		
Active oral corticosteroid use	2.43	1.09–5.45	0.031	ns		
Active use of topical treatment	0.82	0.40–1.69	0.596			

*Low level included elementary school, intermediate level included secondary (vocational) education, and high level included higher (vocational) education.
†Manual/physical labor.
‡Patient underwent 1 prior small or large bowel resection.
§P-HBI > 4 or p-SCCAI > 4.
BMI indicates body mass index; IPAA, ileal puch-anal anastomosis; ns indicates not significant (variables not included in the final equation); Ref, reference.

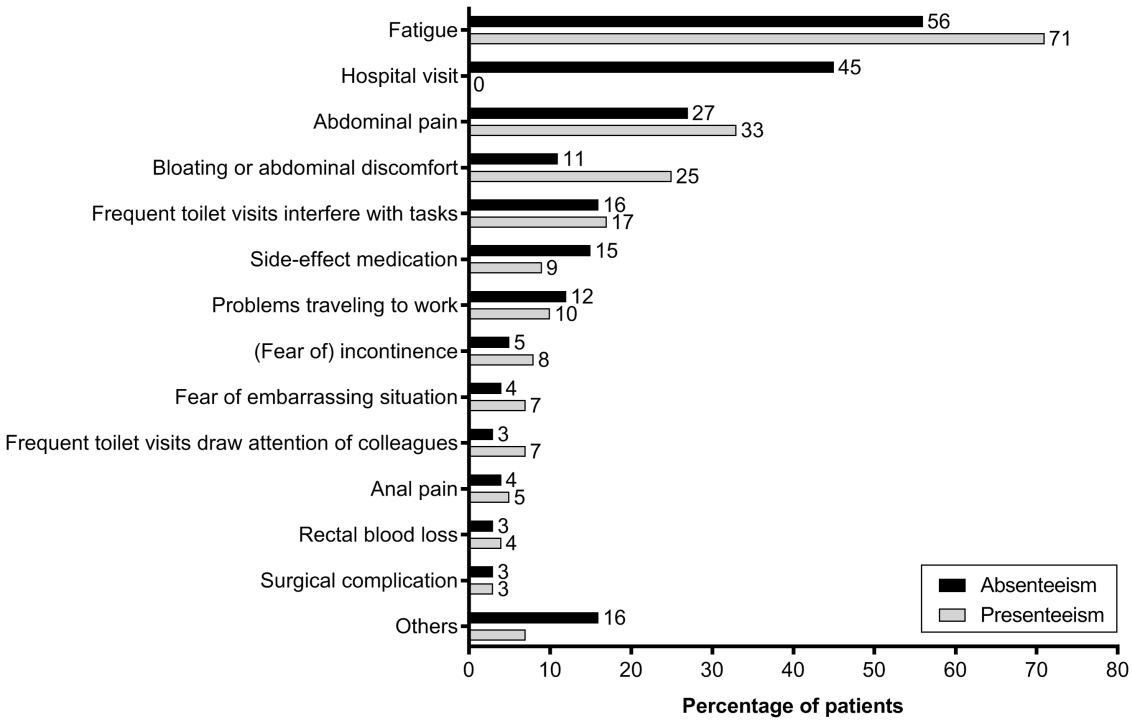

FIGURE 3. Patient-reported IBD-related reasons for WP loss. Patient-reported reasons for WP loss presented as percentages of the total number of patients who reported absenteeism or presenteeism. Patients could have answered with more than 1 response as a reason for their absenteeism or presenteeism. Other reasons included for absenteeism: recovery of recent bowel or fistula surgery, visit of reintegration coach, stoma leakage, CD-related trauma therapy psychologist, partial work disability, recovery after exacerbation, adverse effect of medical therapy used for complications of other IBD therapy, viral infection/illness and headache. Other reasons included for presenteeism: concentration problems, recovery after fistula surgery, physical limitations because of stoma (eg, heavy lifting), fistula, stoma leakage, frequent changing of stoma bag, sweating, urgency, headache, arthralgia, myalgia, aggravated tinnitus, CD-related trauma, partial work disability, adverse effect of medical therapy used for complications of other IBD therapy and visual impairment.

frequent toilet visits (17%), and adverse effects of IBD medication (9%) were other frequently reported reasons for presenteeism.

Fatigue and HRQL

A mean (SD) total fatigue (MFI) score of 51 (17) was found (Supplementary Table 4). The highest mean subscores were found for general fatigue (13 [4]). A mean score of 10 (4) was observed for physical fatigue and for mental fatigue, and the lowest score of 9 (4) was found for both reduced activity and reduced motivation. Patients in the third-class biologic group had the highest total fatigue score of 67 (20), and patients in the immunomodulator- and biologic-naïve group had the lowest score (48 [16]). Severe fatigue was reported by 232 out of 510 patients (46%) (Fig. 2) and was more prevalent in patients with CD than in patients with UC (51% vs 40%, respectively; $P = 0.012$). In the total IBD group, the mean (SD) SIBDQ score was 55 (9), and 131 out of 510 (26%) patients reported reduced HRQL (Fig. 2, Supplementary Table 5). The lowest SIBDQ score and the largest proportion of patients with reduced HRQL were found in the third-class biologic group (49 [6] and 67%, respectively). Patients who were immunomodulator- and biologic-naïve reported the highest SIBDQ score and represented the lowest proportion of patients with reduced HRQL (56 [8] and 19%, respectively). A higher proportion of patients with CD reported reduced HRQL compared with patients with UC (32% vs 19%; $P = 0.001$). Reduced HRQL and fatigue were significantly correlated with higher percentages of WP loss ($r = –0.63$; $P < 0.001$ and $r = 0.53$; $P < 0.001$, respectively) (Fig. 4A, B).

Predictors of severe fatigue and reduced HRQL

Clinical disease activity (OR = 3.5; 95% CI, 2.1-5.9), arthralgia (OR = 2.1; 95% CI, 1.4-3.3), and corticosteroid use (OR = 2.8; 95% CI, 1.2-6.6) were independent predictors of severe fatigue in the total cohort reaching statistical significance (Supplementary Table 6). A disease duration of 10 years or more was found to be associated with a lower incidence of severe fatigue (OR = 0.7; 95% CI, 0.5-1.0). Overweight (body mass index > 25) patients (OR = 2.1; 95% CI, 1.2-3.4), patients with arthralgia (OR = 2.3; 95% CI, 1.4-3.8) or with disease activity (OR = 10.3; 95% CI, 5.9-17.9), and patients treated with ustekinumab (OR = 4.0; 95% CI, 1.0-16.1) were found to have a significantly higher incidence of reduced HRQL in multivariable regression analysis (Supplementary Table 7).

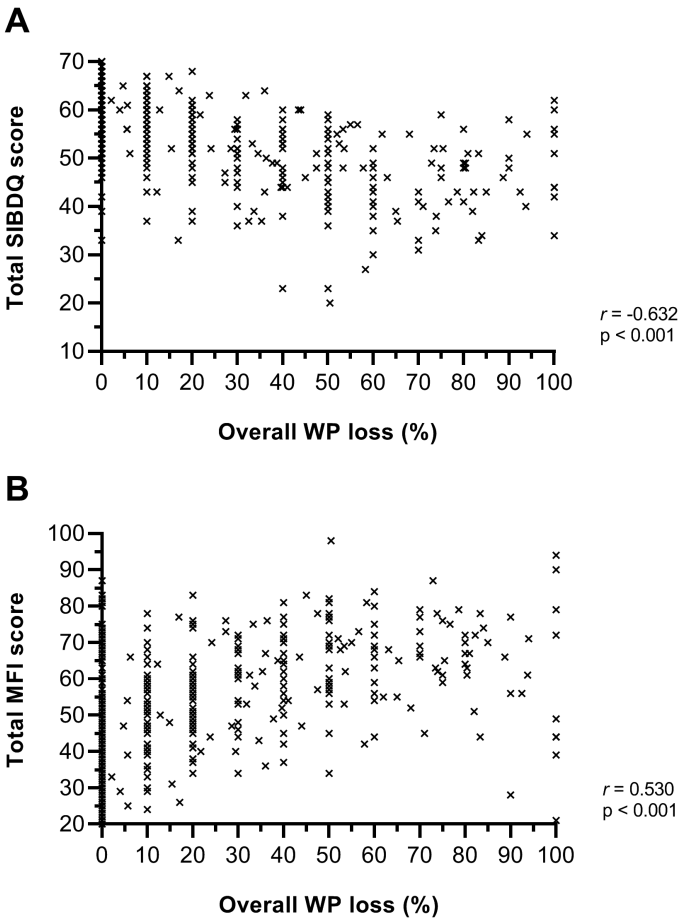

FIGURE 4. Correlation of patient-reported outcomes. A, The SIBDQ score. Quality of life inversely correlated with WP loss (Spearman correlation coefficient = –0.632; $P < 0.001$). B, The MFI score. Fatigue significantly correlated with WP loss (Spearman correlation coefficient = 0.530; $P < 0.001$).

Patients who used 5-ASA (OR = 0.5; 95% CI, 0.3-0.9) or with a disease duration of 10 years or more (OR = 0.5; 95% CI, 0.3-0.9) had a significantly lower incidence of reduced HRQL. In patients with UC, anti-TNF use was found to be an additional independent predictor associated with severe fatigue (OR = 2.9; 95% CI, 1.3-6.6) and reduced HRQL (OR = 4.0; 95% CI, 1.4-10.8) (Supplementary Tables 8, 9).

Indirect Costs

Mean (SD) costs per patient per year for absenteeism, presenteeism, and overall WP loss were €1738 (5505), €5478 (8629), and €6597 (9987), respectively (Fig. 5, Supplementary Table 10). The highest mean indirect costs resulting from overall WP loss were found for patients using second- or third-class biologic treatment (€8756 [9442] and €19,468 [16,807]), and the lowest costs were found for immunomodulator- and biologic-naïve patients (€4756 [10,898]). Mean costs were significantly higher for patients with CD and UC with active disease (€14,619 [12,636]) and for patients with CD with active perianal disease (€15,495 [16,223]) compared with patients with quiescent disease (€4415 [7871]) and patients with CD without active perianal disease (€6949 [9745]), with a mean difference (95% CI) of €10,203 (95% CI, 8261-12,146; $P < 0.001$) and €8546 (95% CI, 4397-12,696; $P < 0.001$), respectively. Although not significantly different, mean (SD) indirect costs were lower for patients using 5-ASA agents (both as monotherapy and as concomitant treatment with other IBD therapies; €5482 [9981]) compared with patients not receiving 5-ASA treatment (€7177 [9953]), with a mean difference (95% CI) of –€1695 (95% CI, –3508 to 117; $P = 0.067$). Patients with reduced HRQL (€13,670 [11,377]) or those reporting severe fatigue (€10,178 [11,157]) were accountable for significantly higher mean indirect costs than were patients with normal HRQL (€4095 [8121]) or without severe fatigue (€3548 [7700]), with a mean difference (95% CI) of €9575 (95% CI, 7767-11,384; $P < 0.001$) and €6630 (95% CI, 4977-8283; $P < 0.001$), respectively.

DISCUSSION

Overall WP loss was reported by approximately 50% of employed patients with IBD. Absenteeism, presenteeism, and overall WP loss resulted in costs of €1738, €5478, and €6597 per patient per year, respectively. In comparison, a Danish population-based study recently showed median total indirect costs per IBD patient per year of approximately €2600 (including costs of sick leave, unemployment benefits, and lost taxes, but excluding presenteeism).[15] In our employed IBD population, we found that WP loss generated significant health care costs mainly caused by "on-the-job productivity loss" (presenteeism). Severe fatigue and reduced quality of life were important reasons for WP loss, thereby driving indirect costs. Immunomodulator- and biologic-naïve patients had the lowest overall disease burden (indicated by WP loss, fatigue, and quality of life outcome measures), likely reflecting a mild disease course. On the other side of the spectrum were patients who used second- or third-class biologic treatment. In particular, patients with CD using ustekinumab as a third-class biologic displayed the highest disease burden, indicating a more aggressive disease course.

As expected, several disease severity aspects (including disease activity and extraintestinal manifestations) were associated with impaired patient-reported outcomes (ie, WP loss, fatigue, and reduced HRQL). However, in contrast to prior studies no association between anti-TNF use and severe WP loss, fatigue, or poor quality of life was found in the entire cohort.[12, 31] Yet subgroup analyses in patients with UC revealed an association between anti-TNF use and severe WP loss, severe fatigue, and reduced HRQL. This result may be explained by the fact that no third-class agent was registered for UC when our study was conducted. Hence, patients with UC using anti-TNF treatment may reflect a more severe disease group compared to patients with CD using anti-TNF agents. In addition,

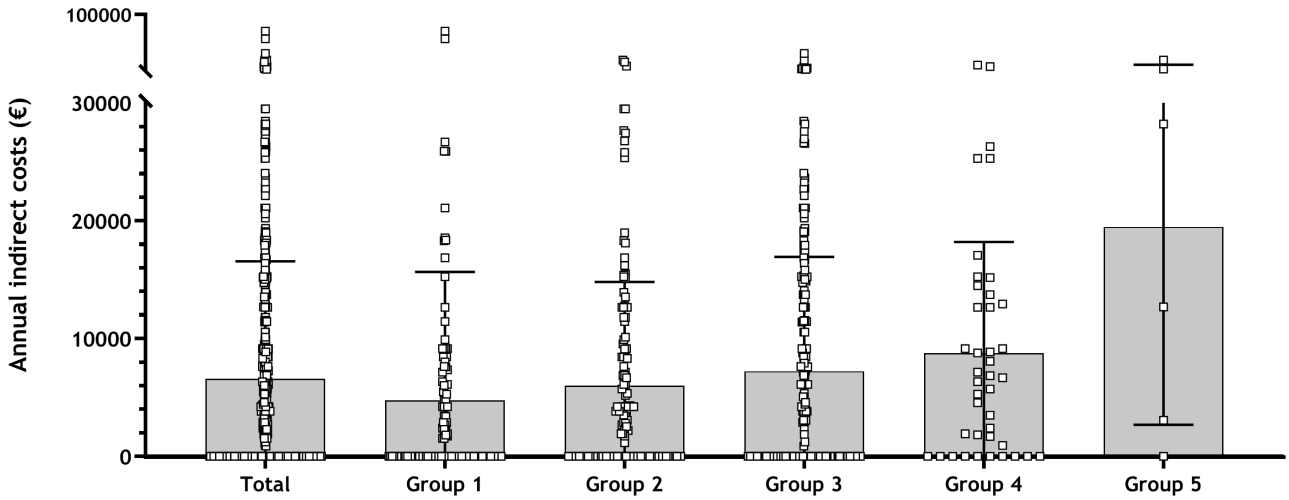

FIGURE 5. Indirect costs (€) per patient per year because of overall WP loss. Grey box and error bars indicate mean and SD of indirect costs per treatment group, respectively. Group 1, immunomodulator- and biologic-naïve; Group 2, biologic-naïve; Group 3, first-class biologic; Group 4, second-class biologic; Group 5, third-class biologic.

a significantly higher incidence of reduced HRQL was shown for patients with CD using ustekinumab. Patients in the third-class biologic group (consisting solely of patients with CD using ustekinumab or vedolizumab) reported the worst outcomes with regard to WP loss, fatigue, and reduced HRQL. These findings support the idea that the type of treatment that patients were using reflected their disease severity and refractoriness. The third-class biologic group also reflected the highest proportion of patients with clinical disease activity and active perianal disease, and these 2 factors were found to be associated with severe WP loss.

Patients could only participate if they were in paid labor, and patients with complete work disability were excluded. Therefore, it is possible that patients with more severe and long-standing disease were excluded. This possibility may explain the different risk factors that were found in a Dutch nationwide web-based survey in patients with IBD that used work disability as an outcome measure.[5] In that study, associations were found between higher age, lower education level, depression, chronic back pain, joint manifestations, and disease severity (indicated by a penetrating disease course and prior bowel-related surgery) and work disability.[5]

In the present study, a large cohort of patients with IBD were enrolled at both academic and nonacademic centers, and patient-reported outcome measures and patient phenotypic data were collected in detail at the patient level. We were thus able to accurately study the disease burden and associated costs in employed patients with IBD. Our study is one of the few that has investigated the indirect costs incurred from both absenteeism and presenteeism, because most studies have analyzed indirect costs from work disability registries, lacking sufficient WP loss data related to presenteeism.[15, 16, 32] Moreover, this is the first study to assess second- and third-class biologics as potential treatment-related predictors in patients with IBD for WP loss, fatigue, and reduced HRQL, although patient numbers were relatively small. Note that our results may underestimate the amount of WP loss in other countries because of differences in socioeconomic circumstances and social policies. For example, more than 50% of our cohort consisted of part-time working patients with IBD, and health insurance is mandatory in the Netherlands. In contrast, in the United States a full-time employment contract of at least 40 hours per week is often necessary to obtain commercial health insurance.

As previously mentioned, one potential limitation is that we only included patients in paid labor, which may have excluded patients with severe and long-standing disease. In addition, the voluntary fashion of participation may have induced selection bias: it is possible that a higher proportion of patients with severe disease participate in these types of studies. Furthermore, yearly indirect costs were estimated based on calculations using the WPAI survey, in which WP loss was measured in the previous week. However, in these calculations we corrected for age, sex, and individual contract hours, which contributed to more accurate estimations. In line with this notion, we relied on patient-reported outcomes to measure disease activity because objective biomarkers such as fecal calprotectin and C-reactive protein were available in a limited number of patients. Therefore, clinical disease activity measured in this study may represent the patients' experience with their disease (disease burden) or functional symptoms rather than actual disease activity, especially in CD. Last, another limitation is the cross-sectional study design, in which no correction for disease severity could be made. However, these findings will be validated in a prospective fashion using follow-up data from the ongoing WORK-IBD study.

This study underscores the importance and disabling impact of fatigue in IBD, affecting patients with active and inactive disease. It was shown that fatigue is associated with a considerable disease burden and high indirect costs. In line with that notion, the most frequently reported reason for absenteeism and presenteeism by patients with IBD was fatigue. The etiology and pathophysiology of fatigue in IBD is complex and many possible causes have been described, including circulating inflammatory cytokines, nutritional deficiencies and anemia, sleep disturbance, altered metabolomic profiles, microbiota changes, and physical inactivity.[33] Arthralgia was found to be an independent predictor of severe fatigue in our cohort, confirming earlier work.[34] In addition, we found 2 other predictors for severe fatigue: disease activity and corticosteroid use, which both may be attributed to a high amount of circulating inflammatory cytokines because of active disease.

Evidence-based therapies for fatigue in patients with IBD primarily include psychological interventions, such as cognitive-behavioral therapy and solution-focused therapies, the last focusing on practical solutions to better deal with fatigue.[35, 36] Physical therapy has been studied as a complementary therapy in IBD, showing improvement in quality of life.[37-39] In other diseases, such as chronic fatigue syndrome and cancer, physical therapy has been demonstrated to be beneficial with regard to fatigue.[40, 41] A meta-analysis of placebo-controlled trials has shown the beneficial effects of microbiota-directed therapies (such as probiotic supplementation) in depression, and a pilot study revealed a reduction in fatigue levels within 2 weeks in patients suffering from chronic fatigue syndrome.[42, 43]

CONCLUSIONS

In conclusion, WP loss and indirect costs in the employed IBD population are predominantly associated with disease activity/severity and a high disease burden (indicated by reduced HRQL and fatigue). Fatigue seems to be the most relevant factor accounting for WP loss, leading to considerable indirect costs in the working IBD population. However, because of the complex etiology and pathophysiology of fatigue in IBD it will be challenging to manage fatigue to reduce the disease burden in these patients. A multidimensional approach is likely required to reduce the disease burden and its associated indirect costs, which should primarily focus on tight disease control, recognition and treatment of extraintestinal manifestations (mainly arthralgia and perianal disease), and adequate management of fatigue.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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REFERENCES

1. IsHak WW, Pan D, Steiner AJ, et al. Patient-reported outcomes of quality of life, functioning, and GI/psychiatric symptom severity in patients with inflammatory bowel disease (IBD). *Inflamm Bowel Dis.* 2017;23:798–803.
2. Bernklev T, Jahnsen J, Henriksen M, et al. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2006;12:402–412.
3. Ananthakrishnan AN, Weber LR, Knox JF, et al. Permanent work disability in Crohn's disease. *Am J Gastroenterol.* 2008;103:154–161.
4. Mandel MD, Michael MD, Bálint A, et al. Work disability and productivity loss in patients with inflammatory bowel diseases in Hungary in the era of biologics. *Eur J Health Econ.* 2014;15 Suppl 1:S121–S128.
5. van der Valk ME, Mangen M-JJ, Leenders M, et al. Risk factors of work disability in patients with inflammatory bowel disease—a Dutch nationwide web-based survey: work disability in inflammatory bowel disease. *J Crohns Colitis.* 2014;8:590–597.
6. Zand A, van Deen WK, Inserra EK, et al. Presenteeism in inflammatory bowel diseases: a hidden problem with significant economic impact. *Inflamm Bowel Dis.* 2015;21:1623–1630.
7. Siebert U, Wurm J, Gothe RM, et al.; Swiss IBD Cohort Study Group. Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the Swiss inflammatory bowel disease cohort study. *Inflamm Bowel Dis.* 2013;19:847–855.
8. van der Have M, Brakenhoff LKPM, van Erp SJH, et al. Back/joint pain, illness perceptions and coping are important predictors of quality of life and work productivity in patients with inflammatory bowel disease: a 12-month longitudinal study. *J Crohns Colitis.* 2015;9:276–283.
9. De Boer AGEM, Bennebroek Evertsz' F, Stokkers PC, et al. Employment status, difficulties at work and quality of life in inflammatory bowel disease patients. *Eur J Gastroenterol Hepatol.* 2016;28:1130–1136.
10. Yoon JY, Shin JE, Park SH, et al. Disability due to inflammatory bowel disease is correlated with drug compliance, disease activity, and quality of life. *Gut Liver.* 2017;11:370–376.
11. Mesterton J, Jönsson L, Almer SH, et al. Resource use and societal costs for Crohn's disease in Sweden. *Inflamm Bowel Dis.* 2009;15:1882–1890.
12. Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. *J Crohns Colitis.* 2017;11:165–174.
13. van der Valk ME, Mangen M-JJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. *Gut*. 2014;63:72–79.
14. Burisch J, Vardi H, Pedersen N, et al.; EpiCom Group. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom study. *Inflamm Bowel Dis.* 2015;21:121–131.
15. Lo B, Vind I, Vester-Andersen MK, et al. Direct and indirect costs of inflammatory bowel disease: ten years of follow-up in a Danish population-based inception cohort. *J Crohns Colitis.* 2020;14:53–63.
16. Kawalec P. Indirect costs of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. A systematic review. *Arch Med Sci.* 2016;12:295–302.
17. Shafer LA, Walker JR, Restall G, et al. Association between IBD disability and reduced work productivity (presenteeism): a population-based study in Manitoba, Canada. *Inflamm Bowel Dis.* 2019;25:352–359.
18. Anon. *Castor Electronic Data Capture*. Amsterdam, the Netherlands: Ciwit B.V.; 2018. https://www.castoredc.com/.
19. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics.* 1993;4:353–365.
20. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res.* 1995;39:315–325.
21. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol.* 1996;91:1571–1578.
22. Bennebroek Evertsz' F, Nieuwkerk PT, Stokkers PC, et al. The patient simple clinical colitis activity index (P-SCCAI) can detect ulcerative colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. *J Crohns Colitis.* 2013;7:890–900.
23. Bennebroek Evertsz' F, Hoeks CC, Nieuwkerk PT, et al. Development of the patient Harvey Bradshaw index and a comparison with a clinician-based Harvey Bradshaw index assessment of Crohn's disease activity. *J Clin Gastroenterol.* 2013;47:850–856.

24. M. Reilly Associates Inc. WPAI scoring. 2002. http://www.reillyassociates.net/WPAI_Scoring.html. Accessed December 1, 2019.
25. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie.* 2003;26:140–144.
26. Jowett SL, Seal CJ, Phillips E, et al. Defining relapse of ulcerative colitis using a symptom-based activity index. *Scand J Gastroenterol.* 2003;38:164–171.
27. Higgins PD, Schwartz M, Mapili J, et al. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut.* 2005;54:782–788.
28. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw index. *Inflamm Bowel Dis.* 2006;12:304–310.
29. Statistics Netherlands. *Werkgelegenheid; banen, lonen, arbeidsduur, SBI2008*; kerncijfers. 2017. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/81431ned/table?ts=1587631236576.
30. Statistics Netherlands. *Beloning en arbeidsvolume van werknemers*; bedrijfstak, nationale rekeningen. 2017. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/84165NED/table?ts=1587642964325.
31. Vogelaar L, van't Spijker A, van Tilburg AJ, et al. Determinants of fatigue in Crohn's disease patients. *Eur J Gastroenterol Hepatol.* 2013;25:246–251.
32. Kuenzig ME, Lee L, El-Matary W, et al. The impact of inflammatory bowel disease in Canada 2018: indirect costs of IBD care. *J Can Assoc Gastroenterol.* 2019;2:S34–S41.
33. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nat Rev Gastroenterol Hepatol.* 2019;16:247–259.
34. Solberg IC, Lygren I, Jahnsen J, et al.; IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol.* 2009;44:431–440.
35. McCombie AM, Mulder RT, Gearry RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohns Colitis.* 2013;7:935–949.
36. Vogelaar L, van't Spijker A, Timman R, et al. Fatigue management in patients with IBD: a randomised controlled trial. *Gut.* 2014;63:911–918.
37. de Souza Tajiri GJ, de Castro CL, Zaltman C. Progressive resistance training improves muscle strength in women with inflammatory bowel disease and quadriceps weakness. *J Crohns Colitis.* 2014;8:1749–1750.
38. Klare P, Nigg J, Nold J, et al. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. *Digestion.* 2015;91:239–247.
39. Eckert KG, Abbasi-Neureither I, Köppel M, et al. Structured physical activity interventions as a complementary therapy for patients with inflammatory bowel disease—a scoping review and practical implications. *BMC Gastroenterol.* 2019;19:115.
40. Puetz TW, Flowers SS, O'Connor PJ. A randomized controlled trial of the effect of aerobic exercise training on feelings of energy and fatigue in sedentary young adults with persistent fatigue. *Psychother Psychosom.* 2008;77:167–174.
41. Vermaete N, Wolter P, Verhoef G, et al. Physical activity, physical fitness and the effect of exercise training interventions in lymphoma patients: a systematic review. *Ann Hematol.* 2013;92:1007–1021.
42. Huang R, Wang K, Hu J. Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. *Nutrients.* 2016;8:483.
43. Sullivan A, Nord CE, Evengård B. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. *Nutr J.* 2009;8:4.