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ORIGINAL RESEARCH

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Patient-reported symptoms are a more reliable predictor of the societal burden compared to established physician-reported activity indices in inflammatory bowel disease: a cross-sectional study

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ABSTRACT

Background: The societal burden of inflammatory bowel diseases (IBD) is not well documented, and further studies are needed to quantify the costs of the disease state. Thus, the aim was to estimate the societal burden and identify its predictors.

Methods: A cross-sectional questionnaire-based study complemented by objective data from patient medical records was performed for patients with Crohn's disease (CD) and ulcerative colitis (UC).

Results: We analyzed data from 161 patients (CD: 102, UC: 59). The overall work impairment reached 15.4%, 11.2% vs. 28.8% without/with self-reported symptoms ($p = 0.006$). Daily activity impairment was 19.3%, 14.1% vs. 35.6% ($p < 0.001$). The disability pension rate was 28%, 23% vs. 44% ($p = 0.012$). The total productivity loss due to absenteeism, presenteeism, and disability amounted to 7,673 €/patient/year, 6,018 vs. 12,354 €/patient/year ($p = 0.000$). Out-of-pocket costs amounted to 562 €/patient/year, 472 vs. 844 €/patient/year ($p = 0.001$). Self-reported symptoms were the strongest predictor of costs ($p < 0.001$).

Conclusion: We found a high societal burden for IBD and a significant association between patient-reported disease symptoms and work disability, daily activity impairment, disability pensions, and out-of-pocket costs. Physician-reported disease activity is not a reliable predictor of costs except for out-of-pocket expenses.

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absenteeism; Crohn's disease; out-of-pocket costs; presenteeism; productivity costs; ulcerative colitis

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are two forms of inflammatory bowel disease (IBD). They are lifelong multifactorial idiopathic disorders characterized by chronic inflammation of the small intestine and/or colon. IBD affects young adults during their productive age and profoundly impacts their quality of life and work productivity [1,2]. These productivity losses are related to missed work (i.e. temporary, chronic, or permanent absenteeism) or reduced performance at work due to health problems (presenteeism). In addition to paid work, decreased patient productivity affects other daily activities, e.g. household work, informal care, volunteering, and leisure activities [3].

Despite the high economic burden, there is currently limited data assessing productivity loss in paid and unpaid work due to IBD. Recently, a systematic review by Kawalec et al. [4] showed high heterogeneity in published data concerning work productivity of IBD patients. According to eleven studies published between 1994 and 2014, yearly indirect costs due to lost productivity and sick leave alone ranged from $1,159 to $14,136 in CD patients and $926 to $6,583 in UC patients. A data meta-analysis could not be performed due to the heterogeneity of the indirect cost components; the need for further research was stressed in the review's conclusion.

Another recent systematic literature review of real-world data focused only on ulcerative colitis [5]. The review results showed that the indirect costs of UC are not well documented in the literature, and further studies are needed to quantify these costs per disease state [5]. Finally, there is currently no evidence describing the socioeconomic burden of CD and UC in the Czech Republic.

Standard practice guidelines recommend using the Harvey-Bradshaw Index (HBI), and the partial Mayo (pMayo) score to determine disease activity [6]. To what extent these indices correlate with patient-reported disease activity or impairment of work productivity and daily activities is unknown.

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The societal perspective (apart from the usual healthcare payer perspective) has recently been incorporated in assessing orphan medicinal products in the Czech Republic. However, a precise methodology for societal burden estimations has not yet been developed.

This observational cross-sectional study aimed to estimate the burden of IBD in the Czech Republic from a societal perspective using patient questionnaires combined with simultaneous assessments by gastroenterologists. The primary objective was the identification of predictors of work productivity and activity impairment, productivity costs, and out-of-pocket costs related to IBD. The final objective of this study was to propose a methodology for societal burden estimation.

2. Patients and methods

2.1. Study design

The study was designed as a cross-sectional survey. Data were collected using electronic patient questionnaires in two specialized IBD centers providing biological therapy in the Czech Republic from 4/2021 to 3/2022. Physician assessment and data from the medical records were used to complement patient questionnaires. Inclusion criteria were: 1) verified diagnosis of CD/UC, 2) study participation and data processing consent, and 3) age ≥ 18 years. Only fully completed questionnaires were assessed; other exclusion criteria were not specified. The study was approved by the ethics committee of the ISCARE a.s. Clinical Center under the identifier 2021/Ia and the ethics committee of the České Budějovice Hospital under the identifier 111/21. Participation in the study was voluntary and anonymous.

First, disease severity was assessed by patients, i.e. patients reported the presence or absence of disease symptoms. Second, physician-reported disease activity was classified according to Harvey-Bradshaw Index (CD): remission < 5, mild: 5–7, moderate 8–16, severe >16, and the pMayo score (UC): remission < 2, mild: 2–4, moderate: 5–7, severe: >7 [7].

The patient questionnaires collected data describing patient demographics and clinical characteristics, time spent on visits to treatment centers and treatment-related lost productivity, social transfer costs, out-of-pocket expenditures, and a standardized Czech version of the WPAI (work productivity and activity impairment) questionnaire assessing absenteeism, presenteeism, and non-paid daily activities [8]. Data describing clinical activity indices (Harvey-Bradshaw Index for CD and partial Mayo score for UC), Montreal classification of the disease, biological and other therapy, main laboratory findings (C-Reactive Protein, fecal calprotectin), and previous major surgery were collected from medical records.

2.2. Data analysis and statistical methods

The questionnaires were checked for duplicates. Participants with IBD had to (1) be registered at an IBD treatment center and (2) have internet access to complete the electronic form on a computer or mobile device.

Statistical analysis was performed in R and STATA version 15 (StataCorp LLC, Texas). Comparisons between groups were performed using the Mann-Whitney U-test and chi-square tests. The significance level was set at $\alpha = 0.05$. Descriptive data analysis was performed for the whole population and contrasted for the two subpopulations, i.e. with or without disease symptoms (by patient-reported remission/active disease) or physician-reported remission/active disease. Differences between different variables were adjusted using multivariate linear regression, specifically, the ordinary least squares linear model (Stata command regress).

Reporting of the study is in line with the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) [9].

2.3. Assessment of work productivity

A validated Czech version of the WPAI questionnaire was used to evaluate impaired productivity (both paid and unpaid). It was composed of 6 items that can be answered as free text or on an 11-point scale. The questionnaire assesses absenteeism, presenteeism, and non-paid daily activities impairment during the last month. Based on these answers, the time lost due to health issues was assessed. This questionnaire was previously used and is generally recommended for measuring work outcomes in observational studies that include patients with IBD [10–15].

Absenteeism is defined as employment time lost due to illness. Presenteeism describes work productivity/performance limitations during time spent at work due to illness. The disease impacts work quality (rigorousness, conscientiousness, mistakes, task repetition) as well as work quantity (slow working pace, more breaks between tasks). Both absenteeism and presenteeism are expressed as percentages, where 20% equals one lost day from 5 workdays.

The evaluation of productivity loss was measured in two ways. In the first case, productivity loss was considered only in work-active patients (i.e. those who answered YES to question 1 on the WPAI questionnaire). Thus, all work-inactive patients were excluded, and only absenteeism, presenteeism, and overall work impairment were assessed in the analysis.

In the second case, patients with disability pensions were included in the overall assessment of productivity loss. The results show the overall impact on the total loss of societal productivity. We considered three levels of disability pension as defined by law (Act No. 306/2008 Coll., § 39 [16]), corresponding to 42%, 60%, and 85% productivity loss in patients with 1st-degree, 2nd-degree, and 3rd-degree disability, respectively [17]. A physician regularly validates the corresponding productivity loss caused by the disease.

Indirect costs due to lost work productivity were calculated using the human capital approach (HCA) [18]. The friction cost approach (FCA) was used in the sensitivity analysis. The maximum calculated duration in the human capital approach and friction cost method was 12 and 6 months, respectively. For absenteeism, the costs were calculated by multiplying the number of lost hours per month by the average gross hourly wage in 2021 (309 CZK, i.e. 12.04 € [3,19] including employment taxes) by the number of months. To estimate the cost of presenteeism, we multiplied the average hours actually worked per month by the presenteeism score. The resulting

hours lost due to presenteeism were multiplied by the average gross hourly wage and the number of months. For disability, we multiplied the average gross wage by 0.42, 0.60, and 0.85 for 1st-degree, 2nd-degree, and 3rd-degree disability, respectively [16,17,20].

3. Results

3.1. Participants

One hundred sixty-two patients fully completed the questionnaires. For one patient, medical records were not available. Hence, 161 questionnaires completed by patients and physicians were analyzed (102 patients with CD and 59 patients with UC). Sixteen patients submitted incomplete questionnaires, which were excluded from the analysis. The total productivity costs were assessed in 134 patients that answered YES to question 1 on the WPAI questionnaire or received a disability pension. Absenteeism, presenteeism, and overall work impairment were assessed in 114 patients that answered YES to question 1 on the WPAI questionnaire. Patient flow is depicted in Figure 1.

Patient demographics and clinical characteristics are described in Table 1. The mean age of IBD patients was 41.2 years, and they were diagnosed on average at age 29. More than one-half of the participants (58.4%) were female. The mean disease duration was 13.2 years, with the mean age at symptom presentation of 27.5. Most patients, i.e. 122 out of 161 (75.8%), assessed themselves as having no symptoms. In comparison, 114 (71%) patients were assessed by physicians as being in remission according to pMayo/HBI score. The mean pMayo score reached 2.13 in the IBD population: 0.90 in the subgroup without disease symptoms vs. 4.94 in the subgroup with disease symptoms ($p < 0.000$). The mean HBI score reached 2.83 in the IBD population: 2.30 in the subgroup without disease symptoms vs. 4.90 in the subgroup with disease symptoms ($p < 0.000$). The patient-reported and physician-reported assessment of remission correlated significantly ($p < 0.000$), although not perfectly, with a Kendall´s tau of 0.53 (Table 1).

Most patients (94%) were on biological treatment at the time of assessment, with nearly half (42%) receiving infliximab biosimilar. Only 62 patients (39%) received something other than a biological treatment (mostly azathioprine). There were no significant differences in patient characteristics in the subgroup with/without disease symptoms, apart from clinical disease activity, other than biological treatment, fecal calprotectin levels, and complications. The mean fecal calprotectin reached 327 µg/g in the IBD population: 241 µg/g in the subgroup without disease symptoms vs. 592 µg/g in the subgroup with disease symptoms ($p = 0.0004$). (Table 1).

3.2. Disability pension and work disability

The overall disability pension rate in this IBD population was 28%, 23% vs. 44% without/with self-reported symptoms ($p = 0.012$). The mean yearly disability allowance reached 4,489 € per disabled patient, 4,627 and 4,245 €/patient/year without/

*not working = answered NO to question 1 on the WPAI questionnaire

Figure 1. Flow diagram.

Table 1. Patient characteristics.

	Total (N = 161)	Patient-reported remission (N = 122)	Patient-reported active disease (N = 39)	p-value*
Crohn's disease, n (%)	102 (63%)	81 (66%)	21 (54%)	0.157
Female, n (%)	94 (58%)	69 (57%)	25 (64%)	0.405
Mean age, y (SD, p25, p75, p50)	41.2 (13.11, 31, 49, 39)	41.7 (13.10, 32, 49, 40)	39.8 (13.20, 29, 51, 38)	0.367
Disease duration, y (SD, p25, p75, p50)	13.2 (8.8, 7, 18, 12)	13.3 (8.3, 7, 18, 12)	12.8 (10.5, 5, 17, 10)	0.412
Mean age at presentation, y (SD, p25, p75, p50)	27.5 (10.1, 20, 34, 25)	27.5 (10.2, 21, 34, 27)	27.6 (10.07, 20, 34, 25)	0.962
Mean age at diagnosis, y (SD, p25, p75, p50)	29.0 (10.4, 21, 36, 27)	29.0 (10.7, 21, 37, 27)	28.8 (9.7, 22, 34, 27)	0.937
pMayo score (SD, p25, p75, p50)	2.1 (2.4, 0, 4, 1)	0.9 (1.2, 0, 2, 0)	4.9 (2.3, 4, 6, 5)	< 0.001
HBI score (SD, p25, p75, p50)	2.8 (2.6, 1, 4, 2)	2.3 (2.4, 1, 3, 2)	4.9 (2.7, 3, 6, 5)	< 0.001
Physician-reported remission**, n (%)	114 (71%)	103 (84%)	11 (28%)	< 0.000
Physician-reported mild activity, n (%)	30 (19%)	17 (14%)	13 (33%)	
Physician-reported moderate activity, n (%)	15 (9%)	2 (2%)	13 (33%)	
Physician-reported severe activity, n (%)	2 (1%)	0 (0%)	2 (5%)	
Montreal classification***, n (%)	18 (18%)	16 (20%)	2 (10%)	0.628
A1, n (%)	80 (78%)	61 (75%)	19 (90%)	0.824
A2, n (%)	3 (3%)	3 (4%)	0 (0%)	0.282
A3, n (%)	30 (29%)	23 (28%)	7 (33%)	0.916
B1, n (%)	31 (30%)	26 (32%)	5 (24%)	
B2, n (%)	41 (40%)	32 (40%)	9 (43%)	
B3, n (%)	4 (4%)	3 (4%)	1 (5%)	
L1, n (%)	25 (25%)	23 (28%)	2 (10%)	
L2, n (%)	1 (1%)	0 (0%)	1 (5%)	
L2/L3, n (%)	53 (52%)	40 (49%)	13 (62%)	
L3, n (%)	1 (1%)	1 (1%)	0 (0%)	
L3/L4, n (%)	17 (17%)	13 (16%)	4 (19%)	
L4, n (%)	6 (10%)	4 (10%)	2 (11%)	
E1, n (%)	22 (37%)	16 (39%)	6 (33%)	
E2, n (%)	31 (53%)	21 (51%)	10 (56%)	
E3, n (%)				
Biological treatment, n (%)	152 (94%)	116 (95%)	36 (92%)	0.162
adalimumab, n (%)	14 (9%)	13 (11%)	1 (3%)	
adalimumab biosimilar†, n (%)	14 (9%)	10 (8%)	4 (10%)	
infliximab, n (%)	2 (1%)	1 (1%)	1 (3%)	
infliximab biosimilar†, n (%)	67 (42%)	55 (45%)	12 (31%)	
tofacitinib, n (%)	3 (2%)	2 (2%)	1 (3%)	
ustekinumab, n (%)	22 (14%)	12 (10%)	10 (26%)	
vedolizumab, n (%)	30 (19%)	23 (19%)	7 (18%)	
No biological treatment, n (%)	9 (6%)	6 (5%)	3 (8%)	
Other than biological treatment, n (%)	62 (39%)	42 (34%)	20 (51%)	0.017
azathioprine, n (%)	30 (19%)	23 (19%)	7 (18%)	
azathioprine + prednisone, n (%)	1 (1%)	0 (0%)	1 (3%)	
budesonide, n (%)	2 (1%)	1 (1%)	1 (3%)	
mesalazine, n (%)	11 (7%)	7 (6%)	4 (10%)	
methotrexate, n (%)	6 (4%)	5 (4%)	1 (3%)	
methylprednisolone, n (%)	3 (2%)	0 (0%)	3 (8%)	
prednisone, n (%)	4 (2%)	2 (2%)	2 (5%)	
salazopyrin, n (%)	5 (3%)	4 (3%)	1 (3%)	
No other treatment than biologics, n (%)	99 (61%)	80 (66%)	19 (49%)	
Laboratory findings, mean (SD, p25, p75, p50)	328 (541, 32, 326, 117)	242 (373, 30, 257, 112)	593 (829, 45, 802, 255)	0.018
Fecal calprotectin (µg/g)	4.3 (10.2, 1, 4, 2)	3.8 (10.2, 1, 4, 2)	5.9 (9.4, 1, 5, 2)	0.065
CRP (mg/l)				
Mean BMI, kg/m^2 (SD, p25, p75, p50)	25.3 (4.7, 22, 28, 25)	25.5 (4.9, 22, 28, 25)	24.8 (4.1, 22, 26, 24)	0.443
Smoking, n (%)	17 (11%)	11 (9%)	6 (15%)	0.136
History of surgical treatment	107 (66%)	85 (70%)	22 (56%)	0.101
0 previous major surgery, n (%)	47 (29%)	34 (28%)	13 (33%)	
1 previous major surgery, n (%)	4 (2%)	1 (1%)	3 (8%)	
2 previous major surgeries, n (%)	1 (1%)	1 (1%)	0 (0%)	
3 previous major surgery, n (%)	2 (1%)	1 (1%)	1 (3%)	
4+ previous major surgeries, n (%)				
Presence of complications, n (%)	34 (21%)	19 (16%)	15 (38%)	0.002
Joint disorders, n (%)	16 (10%)	8 (7%)	8 (21%)	
Fistulas, n (%)	4 (2%)	2 (2%)	2 (5%)	
Skin disorders, n (%)	3 (2%)	1 (1%)	2 (5%)	
Hepatobiliary disorders, n (%)	3 (2%)	2 (2%)	1 (2%)	
Eye disorders, n (%)	3 (2%)	1 (1%)	2 (5%)	
Major surgery, n (%)	2 (1%)	1 (1%)	1 (2%)	
Others (not IBD-related), n (%)	15 (9%)	12 (10%)	3 (8%)	

*Differences between groups were assessed using Mann-Whitney and Chi-square tests.

** The disease activity was classified according to Harvey-Bradshaw Index (CD): remission < 5, mild: 5–7, moderate 8–16, severe > 16; and pMayo score (UC): remission < 2, mild: 2–4, moderate: 5–7, severe: > 7.

***Montreal classification for Crohn's disease: Age at diagnosis A1 below 16 y, A2 between 17 and 40 y, A3 above 40 y; L1 ileal, L2 colonic, L3 ileocolonic, L4 isolated upper disease, B1 non-stricturing, non-penetrating, B2 stricturing, B3 penetrating; Montreal classification of the extent of ulcerative colitis (UC): E1 ulcerative proctitis, E2 left-sided UC (distal UC), E3 extensive UC (pancolitis).

†Adalimumab biosimilars: Hulio, Imraldi; Infliximab biosimilars: Remsima and Flixabi

SD: Standard Deviation, p25: 25th percentile, p75: 75th percentile, p50: median (50th percentile), CRP: C-reactive protein, BMI: body mass index; IBD: inflammatory bowel disease.

with self-reported symptoms, respectively. No patient received any other transfer payments (state benefits etc.) related to IBD.

Among employed patients, mean absenteeism reached 6.2% (SD: 18.0) overall; 3.3% (SD: 11.4) vs. 15.5% (SD: 29.0) without/with self-reported symptoms, respectively (p = 0.008). Mean presenteeism was 13.2% (SD: 21.5); 9.5% (SD: 18.0) vs. 24.6% (SD: 27.0) without/with self-reported symptoms (p = 0.005). Overall work impairment reached 15.4% (SD: 23.0); 11.2% (SD: 18.6) vs. 28.8% (SD: 30.2) without/with self-reported symptoms (p = 0.006). Daily activity impairment in unpaid activities was 19.3% (SD: 25.2); 14.1% (SD: 21.7) vs. 35.6% (SD: 28.5) without/with self-reported symptoms (p < 0.001). (Figure 2)

Surprisingly, there was no significant difference in productivity between physician-reported remission vs. active disease subgroups, with the only exception being daily activity impairment in unpaid activities. Mean absenteeism reached 4.7% (SD: 15.4) vs. 10.3% (SD: 23.6) in patients with physician-reported remission vs. active disease, respectively (p = 0.162). Mean presenteeism was 11.6% (SD: 20.9) vs. 17.6% (SD: 22.6) in patients with physician-reported remission vs. active disease (p = 0.068). Overall work impairment reached 13.6% (SD: 22.3) vs. 20.3% (SD: 24.5) in patients with physician-reported remission vs. active disease (p = 0.122). Daily activity impairment in unpaid activities was 16.1% (SD: 23.8) vs. 27.2% (SD: 27.1) in patients with physician-reported remission vs. active disease (p = 0.004). (Figure 3)

The average hours worked amounted to 138 hours/patient/month, 148 and 111 hours/patient/month without/with self-reported symptoms, respectively. The average hours lost due to absenteeism was 8 hours/patient/month, 3 and 22 hours/patient/month without/with self-reported symptoms,

Figure 2. Percentage of impairment in work productivity and daily activities according to the patient-reported disease activity.

Figure 3. Percentage of impairment in work productivity and daily activities according to the physician-reported disease activity.

respectively. The average hours lost due to presenteeism was 15 hours/patient/month, 13 and 20 hours/patient/month without/with self-reported symptoms, respectively.

Average yearly productivity loss due to absenteeism using the human capital approach was 1,168 €/patient/year overall, 480 and 3,183 €/patient/year without/with self-reported symptoms, respectively (p = 0.000). The average cost of presenteeism was 2,111 €/patient/year overall, 1,843 and 2,897 €/patient/year without/with self-reported symptoms, respectively (p = 0.153). The total loss of productivity due to absenteeism, presenteeism, and disability was 7,673 €/patient/year overall, 6,018 and 12,354 €/patient/year without/with self-reported symptoms, respectively (p = 0.000). All results and the corresponding p-values are summarized in Table 2.

According to the multivariate linear regression analysis, self-reported symptoms (i.e. disease activity) were the only independent predictor of patient productivity. Age, disease duration, gender, IBD type, smoking, and BMI had no measurable impact (see Appendix for the detailed regression analysis results).

The crude difference in total productivity cost (in the subgroup with vs. without symptoms) amounted to −6,336 €/patient/year (95% CI: −9,690 to −2,983), while the adjusted difference was equal to −6,689 €/patient/year (95% CI: −10,162 to −3217, p < 0.001). This represents a 51% decrease (54% adjusted) in costs in the subgroup without symptoms (i.e. patient-reported remission). A similar trend was observed for individual components of total productivity costs (see Table 2). The differences were adjusted for age, disease duration, gender, BMI, IBD type, and smoking history.

Notably, there was no significant difference in productivity costs between physician-reported remission vs. active disease subgroups (Table 3). The objectively determined remission was thus not a valid predictor of productivity impairment and related costs. Moreover, not even fecal calprotectin (as a continuous variable) significantly predicted productivity/out-of-pocket costs (see Appendix for multiple regression results). Nevertheless, plasma C-reactive protein (as a continuous variable) was a significant predictor of productivity costs due to WI (p = 0.014) and productivity costs due to presenteeism (p = 0.032). However, the significance level was not reached in total productivity costs (p = 0.152) and absenteeism (p = 0.146).

We also verified whether the HBI and the pMayo score predicted the above-mentioned outcomes when used as continuous variables. Harvey-Bradshaw index (as a continuous

Table 2. Productivity and out-of-pocket costs in patients without/with IBD symptoms.

	Total (SD)	Patient-reported remission	Patient-reported active disease	Difference [95% CI]	p-value*	Adjusted difference [95% CI]**	p-value adjusted**
Productivity costs (A), €/year (SD, p25, p75, p50)	1,168 (3,607, 0, 1,156, 0)	480 (827, 0, 578, 0)	3,183 (6,694, 0, 2,167, 867)	−2,703 [−4,162; −1,245]	0.000	−2,850 [−4,451; −1,249]	0.001
Productivity costs (P), €/year (SD, p25, p75, p50)	2,111 (3,421, 0, 2,600, 0)	1,843 (3,291, 0, 2,500, 0)	2,897 (3,727, 0, 5,316, 159)	−1,054 [−2,505;397]	0.153	−1,401 [−2,983; −180]	0.082
Productivity costs (WI; A + P), €/year (SD, p25, p75, p50)	3,279 (5,132, 0, 3,814, 1,084)	2,323 (3,603, 0, 2,947, 433)	6,081 (7,512, 0, 11,500, 2,889)	−3,758 [−5,838; −1,677]	0.016	−4,251 [−6,538; −1,965]	0.000
Total productivity costs (A + P + D), €/year (SD, p25, p75, p50)	7,673 (9,032, 0, 13,501, 3,005)	6,018 (7,673, 0, 10,553, 2,312)	12,354 (10,902, 2,167, 21,358, 10,553)	−6,336 [−9,690; −2,983]	0.000	−6,689 [−10,162; −3,217]	0.000
Out-of-pocket costs, €/year (SD, p25, p75, p50)	562 (609, 164, 725, 346)	472 (510, 140, 643, 281)	844 (791, 328, 1,076, 655)	−372 [−588; −156]	0.001	−396 [−626; −170]	0.001

*Differences between groups were assessed using Mann-Whitney and Chi-square tests.
**adjusted for age, disease duration, gender, BMI, IBD type, and smoking history

Table 3. Productivity and out-of-pocket costs in patients with physician-reported remission/active disease.

	Total (SD)	Physician-reported remission	Physician-reported active disease	Difference [95% CI]	p-value*	Adjusted difference [95% CI]**	p-value adjusted**
Productivity costs (A), €/year (SD, p25, p75, p50)	1,168 (3,607, 0, 1,156, 0)	807 (2,669, 0, 1,011, 0)	2,093 (5,252, 0, 1,734, 361)	−1,286 [−2,762; 191]	0.087	−1,228 [−2,890; −435]	0.146
Productivity costs (P), €/year (SD, p25, p75, p50)	2,111 (3,421, 0, 2,600, 0)	2,054 (3,640, 0, 2,311, 0)	2,259 (2,830, 0, 4,276, 79)	−206 [−1,624; 1,213]	0.775	−705 [−2,290; −880]	0.380
Productivity costs (WI; A + P), €/year (SD, p25, p75, p50)	3,279 (5,132, 0, 3,814, 1,083)	2,861 (4,733, 0, 3,121, 506)	4,352 (5,984, 0, 6,436, 2,383)	−1,491 [−3,601; 619]	0.164	−1,933 [−4,313; −448]	0.110
Total productivity costs (A + P + D), €/year (SD, p25, p75, p50)	7,673 (9,032, 0, 13,501, 3,005)	6,897 (8,620, 0, 12,865, 2,528)	9,706 (9,867, 159, 15,077, 1,006)	−2,809 [−6,240; 622]	0.108	−3,278 [−6,905; −348]	0.076
Out-of-pocket costs, €/year (SD, p25, p75, p50)	562 (609, 164, 725, 346)	490 (537, 140, 655, 281)	737 (735, 304, 948, 459)	−247 [−453; −41]	0.019	−270 [−492; −48]	0.017

*Differences between groups were assessed using Mann-Whitney and Chi-square tests.
**adjusted for age, disease duration, gender, BMI, IBD type, and smoking history

variable) was a significant predictor of total productivity costs (p = 0.031). However, the significance level was not reached in productivity costs due to absenteeism (p = 0.119), presenteeism (p = 0.939), WI (p = 0.352), or out-of-pocket costs (p = 0.199). The partial Mayo score (as a continuous variable) was a significant predictor of productivity costs due to presenteeism (p = 0.022) and out-of-pocket costs (p = 0.000). However, the significance level was not reached in total productivity costs (p = 0.071), productivity costs due to absenteeism (p = 0.385), and WI (p = 0.092) (data not shown). It thus appears that it is not the definition of 'no disease activity/remission' that makes these indices poor predictors compared to patient-reported remission.

3.3. Out-of-pocket costs

Out-of-pocket costs included patients' payments for medicinal products and medical devices (not covered by health insurance), payments for over-the-counter (OTC) products, disinfection, hygiene supplies, medical services not covered by health insurance (including professional caregiving), and transportation payments as well as other patients' payments related to IBD.

Out-of-pocket costs amounted to 562 €/patient/year overall, 472 vs. 844 €/patient/year without/with self-reported symptoms, respectively (p = 0.001). Out-of-pocket costs were composed of OTC drugs/supplements (162 €/year), travel costs (143 €/year), prescription drugs not covered by insurance (60 €/year), medical services not covered by insurance (45 €/year), disinfection (37 €/year), hygiene supplies (36 €/year), medical devices (36 €/year), and other expenses related to IBD.

The crude difference in out-of-pocket cost (in the subgroup with vs. without symptoms) amounted to −372 €/patient/year (95% CI: −588 to −156), while the adjusted difference was equal to −396 €/patient/year (95% CI: −626 to −170, p = 0.001). This represents a 44% decrease (47% adjusted) in costs in the subgroup without symptoms. The differences were adjusted for age, disease duration, gender, BMI, IBD type, and smoking history.

As opposed to productivity costs, there was a significant difference in the out-of-pocket costs between physician-reported remission vs. active disease subgroups (Table 3). Out-of-pocket costs amounted to 490 vs. 737 €/patient/year in patients with physician-reported remission vs. active disease, respectively (p = 0.019). The crude difference in out-of-pocket cost amounted to −247 €/patient/year (95% CI: −453 to −41), while the adjusted difference was equal to −270 €/patient/year (95% CI: −492 to −48, p = 0.017).

Neither fecal calprotectin nor C-reactive protein significantly predicted out-of-pocket costs associated with IBD (see Appendix for multiple regression results).

4. Discussion

The negative impact of IBD on the workforce in patients with CD or UC was previously shown in studies from other countries [4,14,21,22]. However, this is the first study describing the societal burden associated with IBD in detail, combining comprehensive patient questionnaires with a thorough assessment by a gastroenterologist. In addition, this is the first study assessing the societal burden of CD and UC in the Czech Republic [23]. Moreover, it clearly shows a significant difference in work disability, disability pensions, productivity costs, and out-of-pocket costs in relation to patient-reported symptoms. Notably, no significant difference in productivity costs was shown in relation to physician-reported remission/active disease. Finally, the methodology of societal burden estimation proposed in the study is readily applicable in practice and should be utilized in pricing and reimbursement procedures on a national level.

Our findings correlate with a prospective analysis of two infliximab studies involving 728 patients with mild to severe UC [24]. Greater percentages of patients in remission at week 30 were employed (20.6%) and not receiving disability compensation (58.8%) compared to those in relapse (8.3% and 20.0%, respectively; p < 0.05).

Most published studies focused predominantly on sick leave. Blomqvist et al. [25] was the only study that also covered early retirement, which on average, was 14 years. Only the study by Mesterton [26] included presenteeism, but the results did not specify values. Three studies [27–29] assessed the loss of leisure time, but specific values were usually not reported. Only Bassi et al. [28] describe disrupted social activities (per 6 months) due to IBD, which was 17–20 days on average. The methods used to calculate indirect costs were generally unspecified [25,28–33], making the results difficult to interpret.

Moreover, only seven studies [25,28,30–34] evaluated CD and UC patients. Furthermore, most of these studies are now quite outdated. A more recent publication by Holko et al. [21] analyzed the indirect costs of CD in the Polish population. Kuenzig et al. [35] describe the impact of IBD in Canada but excluded presenteeism. Walter et al. [36] focused on indirect IBD costs in Austria. A recent study identifies the socioeconomic burden of UC in Europe [37]. However, Czechia is not included in the study, out-of-pocket costs are omitted, and the methods used to calculate indirect costs are not specified. Finally, the study lacks the variety of clinical features analyzed in our study.

As recommended in most European countries, indirect costs were calculated using the HCA. However, the HCA can overestimate indirect costs compared to the FCA (friction cost approach). Using the FCA, actual productivity costs are lower because patients with long-term disabilities are replaced with previously unemployed colleagues [3,19]. Concerning short-term absences, the difference in productivity costs depends on the length of the friction period. In case of a friction period longer than the period when the patient is absent from work, the results obtained by HCA and FCA are the same. Nonetheless, FCA was not applied in the base-case because there is a lack of relevant information regarding the length of the friction period in the Czech Republic.

The strength of the study lies in the large sample and diversity of self-reported outcomes, as well as clinical features reported by the attending gastroenterologist. The self-assessment part of the study design reflects disease characteristics from the patients' perspective and eliminates interviewer bias. Moreover, the patient's subjective assessment adequately

reflects their daily reality. On the other hand, patient answers might be influenced by recall, response, or social desirability bias. Therefore, patient-reported disease activity was complemented by a physician using medical records. However, there was no significant difference in productivity costs between physician-reported remission vs. active disease subgroups, as opposed to the self-assessment subgroups. This observation questions the validity of commonly accepted remission definitions using the HBI index and pMayo score.

Interestingly, the patient-reported remission was a more reliable predictor of productivity and costs than objective laboratory parameters. Our findings, therefore, suggest that the absence of symptoms might be the most important target of a cost-effective therapy. However, the conclusion should be drawn carefully due to the study's potential limitations. The absence of significant differences in societal burdens between physician-reported remission and active disease might be caused by the limited sample size. Nevertheless, patient-reported disease activity significantly predicted the societal burden in the same sample.

A study limitation might be a potential sampling or selection bias since all patients were treated in highly specialized IBD centers. Nevertheless, patient characteristics were consistent with previous IBD center-based cohorts, as well as a systematic global analysis of IBD patients [14,38]. For instance, the proportion of females suffering from IBD globally is 57%, while 58% of our study sample was female [38]. Moreover, since most patients in these centers were treated with biological therapy, this study can offer a valuable description of this population, which is in the healthcare payers' interest. Finally, an in-depth analysis of the clinical features of the disease could be performed since patients treated in these centers are thoroughly examined and monitored.

Another possible limitation lies in the cross-sectional study design itself. The goal was to describe the correlation between multiple variables, but we can only speculate about causality. Various confounders could have distorted our reported correlations, i.e. third factors not captured by the study. The adjusted differences, however, are comparable to the crude estimates. We showed that no other measured parameter apart from self-reported symptoms predicts activity and productivity impairment along with the resulting indirect costs. Surprisingly, even physician-reported and laboratory-assessed disease activity was not a significant predictor of productivity costs.

It should be noted that HRQoL assessments were not collected in our study. However, according to the LUCID study by Ruiz-Casas et al. [37], EQ-5D results have low sensitivity to changes in disease severity. They showed that the disease had a relatively small impact on patients' HRQoL. Therefore, we assumed that omitting this aspect was not critically affecting the societal burden estimation.

Further research should include repeated measurements of the described variables, disease severity, and other potential confounders. Thus, causality could be verified despite the presence of time-varying confounders [39,40].

Due to the exploratory nature and limited sample, we decided not to correct for multiplicity testing, yet our hypothesis was confirmed at $p < 0.005$ and from several different perspectives (work impairment, activity impairment, costs, and employment).

5. Conclusions

The study revealed the severe socioeconomic burden associated with IBD, a burden that was significantly predicted by patient-reported disease activity. However, it was not significantly predicted by physician-reported remission (i.e. HBI index and pMayo score). This study indicates that induction and maintenance of remission, defined as an absence of symptoms, can lower indirect costs by more than one-half. It is, therefore, convenient for the state of remission to be verified by the patient's assessment.

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Declaration of interest

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Author contributions

B.Decker: study conception and design, data analysis and interpretation, writing up of the first draft of the paper. J.Tuzil: study design, data analysis and interpretation. M.Lukas, K.Cerna, and M.Bortlik: patient recruitment, data collection. B.Velackova: data analysis, material preparation. B. Pilnackova: administrative back-up, material preparation, data collection. T.Dolezal: study conception and design, supervision of the study. All authors revised and approved the final manuscript.

Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author upon request.

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