Smoking is Associated with Higher Disease-related Costs and Lower Health-related Quality of Life in Inflammatory Bowel Disease

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Abstract

Background and Aims: Smoking affects the course of inflammatory bowel disease [IBD]. We aimed to study the impact of smoking on IBD-specific costs and health-related quality-of-life [HrQoL] among adults with Crohn's disease [CD] and ulcerative colitis [UC].

Methods: A large cohort of IBD patients was prospectively followed during 1 year using 3-monthly questionnaires on smoking status, health resources, disease activity and HrQoL. Costs were calculated by multiplying used resources with corresponding unit prices. Healthcare costs, patient costs, productivity losses, disease course items and HrQoL were compared between smokers, never-smokers and ex-smokers, adjusted for potential confounders.

Results: In total, 3030 patients [1558 CD, 1054 UC, 418 IBD-unknown] were enrolled; 16% smoked at baseline. In CD, disease course was more severe among smokers. Smoking was associated with > 30% higher annual societal costs in IBD (€7,905 [95% confidence interval €6,234 – €9,864] vs €6,017 [€5,186 – €6,946] in never-smokers and €5,710 [€4,687 – €6,878] in ex-smokers, $p = 0.06$ and $p = 0.04$, respectively). In CD, smoking patients generated the highest societal costs, primarily driven by the use of anti-tumour necrosis factor compounds. In UC, societal costs of smoking patients were comparable to those of non-smokers. Societal costs of IBD patients who quitted smoking > 5 years before inclusion were lower than in patients who quitted within the past 5 years (€ 5,135 [95% CI €4,122 – €6,303] vs €9,342 [€6,010 – €12,788], $p = 0.01$). In both CD and UC, smoking was associated with a lower HrQoL.
Conclusions: Smoking is associated with higher societal costs and lower HrQoL in IBD patients. Smoking cessation may result in considerably lower societal costs.

Key Words: Crohn's disease; economic evaluation; health-related quality of life; smoking; ulcerative colitis

1. Introduction

Inflammatory bowel disease [IBD] is an intestinal disorder comprising Crohn's disease [CD] and ulcerative colitis [UC]. Over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD.[1] The chronicity and the relapsing nature of the disease have a debilitating effect on the lives of patients, and entail a high economic burden to society.[2–4]

It has been well established that cigarette smoking is a major environmental factor in the course of IBD. Whereas smoking exerts deleterious effects in CD, beneficial effects have been observed in UC.[5–9] In CD, smoking is associated with flares, hospitalizations, surgical procedures and increased use of immunosuppressive drugs, whereas in UC, smoking has been linked to a reduced corticosteroid utilization and a reduced risk for colectomy.[10–16] Smoking might therefore not only influence health-related quality of life [HrQoL], but might also have opposing economic consequences, from both a healthcare perspective and a societal perspective. To our knowledge, no studies have been performed to estimate the economic impact of smoking in IBD.

The aims of this study were to examine the impact of smoking on IBD-related costs and on HrQoL in adult IBD patients, from healthcare and societal perspectives.

2. Materials and Methods

This study was carried out with the approval of the Medical Ethics Committee [MEC] of the University Medical Centre Utrecht.

2.1. Study design and study population

The COIN-study [Costs Of Inflammatory bowel disease in the Netherlands][2] is a large multicentre cohort study initiated in 2010, aiming to assess direct and indirect IBD-related costs and HrQoL. Patients aged 18 years or older, attending the IBD units from seven university medical centres and seven general hospitals, were eligible for participation. The study design has been described previously in detail.[2]

2.2. Data collection

Participants were invited to fill in a web-based baseline questionnaire, followed by 3-monthly questionnaires. At baseline, demographic data, smoking status, employment status, previous disease course, HrQoL, disease activity scores and data on current fistulas, stomas and pouches were extracted, based on self-report by patients. Patients reported their IBD diagnosis at baseline. Patients were assigned to 'IBD-unknown' when they did not know their IBD subtype, or reported UC with ileal involvement or fistulas. IBD-unknown patients were included in the total IBD population but were not assigned to either the CD or UC group in the outcome data. Used resources, disease course items and HrQoL were collected during 1 year of follow-up.

2.3. Smoking status

Smoking status of all patients was categorized into 'current smokers', 'ex-smokers' and 'never smokers'. From the ex-smoking patients, the date of smoking cessation was obtained.

2.4. Outcome variables

Disease activity was determined by both the presence or absence of self-reported flares and using disease activity scores. For CD and UC, the shortened Crohn's Disease Activity Index and the modified Truelove and Witts Severity Index were employed, respectively.[17,18] Flares were noted based on a single question ['Do you currently have a flare of IBD?'].

Healthcare costs were obtained by multiplying units of self-reported healthcare utilization by their corresponding prices [using Dutch reference prices for health economic studies when appropriate] [Supplementary Table S1, available as Supplementary data at *ECCO-JCC* online].[2,19–21] Healthcare costs consisted of medication use, hospital admissions, surgeries, diagnostic procedures and outpatient clinic visits.

Patient costs included costs such as travel costs and over-the-counter drug use [for example analgesics and vitamins].

Productivity losses were calculated employing the human capital approach, and consisted of self-reported sick leave [absenteeism] of patients and their caregivers from both paid and unpaid [voluntary] work due to IBD-related illness, multiplied by age-and sex-specific mean gross wage income.[19,22]

Total costs, also referred to as societal costs, were calculated by summing healthcare costs, patient costs and productivity losses. For the healthcare perspective only healthcare costs were included, and for the societal perspective all costs were included. The time horizon was 1 year. All costs were expressed in 2014 euros. Of note, the 2014 exchange rate between euros and US dollars was 0.754, and 0.814 when applying purchasing power parity [PPP] approach.[23]

Work, productivity, activity impairment, employment status [employed, fully or partially incapacitated] and the average number of working hours per week were collected at baseline. Furthermore, impairment of work and daily activities was measured by the Work Productivity and Activity Impairment Questionnaire [WPAI].[24] Apart from absenteeism, this questionnaire measures impairment

in work productivity [ie presenteeism], and impairment in ability to perform daily activities other than work [eg shopping, housework, child care, exercising and studying] in the preceding 7 days.

Health-related quality-of-life: to assess disease-specific HrQoL, we used the validated Dutch version of the IBD-Questionnaire [IBDQ][25] which consists of four domains, ie bowel, systemic, social and emotional symptoms. Generic HrQoL was measured by employing the EuroQol EQ-5D-3L instrument[26] which consists of a descriptive system encompassing five dimensions: mobility, self-care, usual activities, pain and depression/anxiety, with three levels of functioning [no, any or severe problems], and the EQ visual analogue scale [VAS]. Health states were scored using the Dutch tariff[27] to obtain EQ-5D-3L summary indices [EQ indices] ranging from 0 [representing death] to 1 [representing full health].

2.5. Statistical analysis

Analyses were performed for the total IBD population and CD and UC population separately. Variables of disease activity were compared between smokers and never-smokers, and smokers and ex-smokers, using chi-square analysis. Mean annual costs [societal and healthcare costs] were calculated by summing the 3-monthly costs of the first four follow-up questionnaires. Costs were presented with 95% confidence intervals [CI], and estimated using non-parametric bootstrap sampling. In order to represent complete annual costs, patients with missing data for cost items during one or more periods of follow-up were not included in this analysis. We performed a sensitivity analysis using multiple imputation techniques[28,29] to assess the impact of missing data during follow-up. Pooled results of five imputations were compared with the complete case analysis data to audit similarity of presented results using Rubin's rule.[29] Univariable and multivariable logistic regression analysis was used to identify predictors for high costs [defined as the 10% patients with the highest total costs]. Multivariable analysis was performed with co-variables with a p –value < 0.10 in the univariable analysis, retaining age and gender in the final selection. Subsequently, costs of smokers, never-smokers and ex-smokers were mutually compared using independent samples t tests. Differences between patients who quitted smoking within and more than 5 years prior to enrolment were further analysed employing the chi-square test or Mann-Whitney U test, when appropriate. A post hoc multivariable analysis was performed to study the impact of 'number of years after smoking cessation' on healthcare costs. Factors with a p-value < 0.10 in the univariable analysis, age, gender and disease duration were incorporated in the multivariable analysis. Percentages of work impairment measured with the WPAI questionnaire were compared between smokers, never-smokers and ex-smokers with chi-square analysis. Univariable and multivariable logistic regression analysis was used to identify predictors for a low HrQoL [defined as the 10% patients with the lowest HrQoL]. Subsequently, variables of HrQoL were compared between smokers, never-smokers and ex-smokers using nonparametric Mann-Whitney U tests and chi-square analysis when normally distributed; p-values < 0.05 were considered statistically significant. All statistical analyses were performed with SPSS version 21.0 [Armonk, NY].

3. Results

3.1. Study population

In total, 3030 [1558 CD, 1054 UC and 418 IBD-unknown] patients were enrolled. Of all patients, 16% smoked at baseline. Smoking was more common in CD patients than in UC patients [21.1% vs 9.0%, p < 0.01]. Characteristics of smoking, never-smoking and ex-smoking CD and UC study participants are shown in Table 1. Main characteristics of the total IBD population are shown in Supplementary Table S2, available as Supplementary data at *ECCO-JCC* online. Smoking CD patients were more often female, were lower educated and were less frequently employed than never-smoking counterparts. Current smoking UC patients were more often unemployed than never-smokers. Ex-smoking CD and UC patients quitted smoking a median of 10 years (interquartile range [IQR] 5 – 18) and 14 years [IQR 8 – 25]) before inclusion. The overall response rate after 1 year of follow-up was 60% in CD and 66% in UC patients. Complete data on costs items covering all four questionnaires were available for 1200 patients. The incidence of current smoking was slightly lower in these 1200 patients compared with all 3030 patients [14.1% vs 17.3%, p = 0.02].

3.2. Disease activity

CD: at baseline, current smokers more frequently had active disease and fistulas, and reported a higher median number of flares in the past than never-smoking CD patients [Table 1]. During 1 year of follow-up, current smokers persistently had higher disease activity scores than never-smokers (baseline: Short-CDAI: median 170 [IQR 128 – 219] vs 142 [IQR 114 – 198], p < 0.01) [Figure 1; Supplementary Table S3, available as Supplementary data at *ECCO-JCC* online]. Adjusted for abdominal surgery in the past, gender and age, current smoking was associated with an increased risk for anti-tumour necrosis factor [TNF] use at t = 3 months (adjusted odds ratio [OR] 1.41 [95% CI 1.00 – 2.00, p < 0.05).

UC: ex-smokers patients more frequently experienced flares than current smokers at baseline [20.4% vs 11.6%, p < 0.05], and both ex-and never-smokers more frequently used steroids than current smokers [p = 0.02 and p < 0.05, respectively] [Table 1]. Overall, disease activity scores did not differ between current smokers and never- or ex-smokers [Figure 1; Supplementary table S3, available as Supplementary data at *ECCO-JCC* online].

3.3. Costs of smoking

IBD: among all covariates, a flare at baseline was the strongest predictor for high societal costs in IBD (adjusted OR of 3.08 [95% CI 1.79 – 5.31, p < 0.01]). Adjusted for demographic data [ie gender, age, employment status, education level] and disease-specific parameters [flares and previous abdominal surgery], current smoking [as compared with never smoking] was associated with high societal costs in the whole IBD population with an OR of 1.92 [95% CI 1.14 – 3.24, p = 0.02] [Table 2]. Further specified, mean annual societal costs were 31% higher in the smoking IBD population than in the never-smoking population (€7,905 [95% CI €6,234 – €9,864] vs €6,017 [€5,186 – €6,946] p = 0.06), and 38% higher than in the ex-smoking population (€5,710 [€4,687 – €6,878], p = 0.04) [Figure 2, Table 3]. Total costs in IBD were mainly driven by healthcare costs [76% of total costs]. Healthcare costs were 40% higher in smokers than in never smokers (€6,381 [95% CI €5,063 – €7,829] vs €4,573 [€4,011 – €5,206], p = 0.01) and 53% higher than in ex-smokers (€4,163 [€3,422 – €4,914], p < 0.01). Of healthcare costs, 65% was caused by the use of anti-TNF compounds in smokers, compared with 56% in never-smokers and 55% in ex-smokers. Patient costs were higher in smoking IBD patients than in never-smokers and ex-smokers [p = 0.02 and p = 0.03, respectively]. There was no difference in productivity losses between smokers, never-smokers and ex-smokers [Table S3]. In our sensitivity analysis, calculated annual costs [ie healthcare,

Table 1. Baseline characteristics, a comparison between smokers, ex-smokers and never-smokers.

	1. Current smokers	2. Never-smokers	3. Ex-smokers	*p*-Value [1 vs 2]	*p*-Value [1 vs 3]
Crohn's disease	*n* = 329	*n* = 781	*n* = 448		
Male gender, *n* [%]	90 [27.4]	306 [39.2]	178 [39.7]	< 0.01	< 0.01
Age: years, mean [SD]	46.4 [12.1]	44.9 [14.2]	50.9 [12.7]	0.10	< 0.01
Low education, *n* [%]	251 [76.3]	451 [57.7]	306 [68.3]	< 0.01	0.02
Currently employed, *n* [%]	141 [57.3]	405 [73.1]	192 [58.7]	< 0.01	0.74
Disease duration: years, median [IQR]	14.9 [7.0 – 24.8]	14.8 [7.0 – 25.8]	17.3 [9.8 – 26.0]	0.87	0.01
Disease localization, *n* [%]				0.10	0.123
Colon	73 [22.2]	227 [29.1]	131 [29.2]		
Small intestine	74 [22.5]	145 [18.6]	87 [19.4]		
Both colon and small intestine	170 [51.7]	379 [48.5]	219 [48.9]		
Unknown	12 [3.6]	30 [3.8]	11 [2.5]		
Flare, *n* [%]	63 [19.1]	98 [12.6]	67 [15.0]	0.004	0.122
Fistula, *n* [%]	62 [18.8]	96 [12.3]	62 [13.8]	0.004	0.060
Stoma or pouch, *n* [%]	53 [16.1]	101 [12.9]	58 [13.6]	0.162	0.332
Abdominal surgery in the past, *n* [%]	182 [55.3]	404 [51.7]	257 [57.4]	0.274	0.570
Number of flares in the past, median [IQR]	7 [3 – 20]	5 [2 – 10]	6 [3 – 15]	< 0.001	0.120
Medication use, *n* [%]*	196 [74.5]	492 [73.5]	280 [75.1]	0.759	0.877
5-ASA	62 [23.5]	150 [22.4]	95 [25.4]	0.727	0.580
Steroids	33 [12.5]	55 [8.2]	46 [12.3]	0.044	0.940
Anti-TNF	69 [26.1]	144 [21.5]	86 [23.0]	0.131	0.362
Immunosuppressive drugs [AZA/6MP/MTX]	97 [36.7]	253 [37.8]	113 [30.2]	0.760	0.084
Ulcerative colitis	*n = 95*	*n = 603*	*n = 358*		
Male gender, *n* [%]	42 [44.2]	284 [47.1]	202 [56.4]	0.60	0.03
Age: years, mean [SD]	46.9 [11.7]	46.9 [13.6]	53.6 [12.0]	1.00	< 0.01
Low education, *n* [%]	58 [61.1]	333 [55.2]	224 [62.6]	0.29	0.79
Currently employed, *n* [%]	60 [73.2]	363 [82.9]	191 [79.9]	0.04	0.20
Disease duration: years, median [IQR]	13.9 [8.8 – 21.2]	12.8 [6.4 – 21.2]	12.4 [5.8 – 20.8]	0.29	0.15
Flare, *n* [%]	11 [11.6]	89 [14.8]	73 [20.4]	0.411	0.049
Stoma or pouch, *n* [%]	10 [10.5]	88 [14.6]	50 [14.0]	0.289	0.379
Abdominal surgery in the past, *n* [%]	17 [17.9]	104 [17.2]	74 [20.7]	0.877	0.548
Number of flares in the past, median [IQR]	5 [3 – 15]	6 [3 – 15]	6 [3 – 15]	0.541	0.268
Medication use, *n* [%][a]	54 [73.0]	420 [79.2]	242 [78.1]	0.219	0.349
5-ASA	44 [59.5]	352 [66.4]	200 [64.5]	0.444	0.417
Steroids	1 [1.4]	40 [7.6]	29 [9.3]	0.047	0.021
Anti-TNF	3 [4.1]	17 [3.2]	15 [4.8]	0.703	0.774
Immunosuppressive drugs [AZA/6MP/MTX]	16 [21.6]	127 [24.0]	60 [19.4]	0.657	0.660

SD, standard deviation; IQR, interquartile range; ASA, aminosalicylic acid; AZA, azathioprine; 6MP, 6-mercaptopurine; MTX, methotrexate; TNF, tumour necrosis factor.

[a]After 3 months of follow-up.

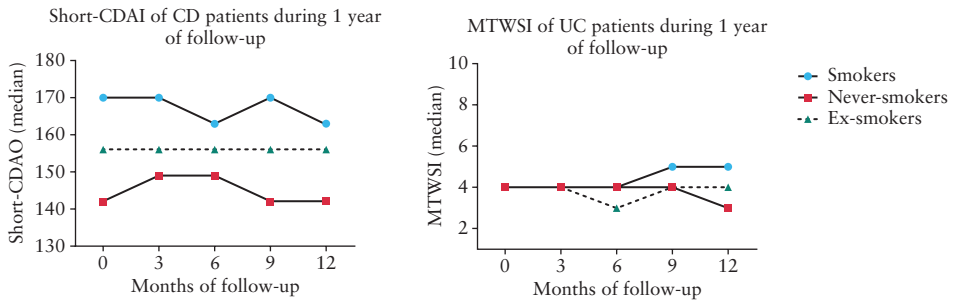

Figure 1. Comparison of disease activity scores of smokers, ex-smokers and non-smokers over one year of follow-up.

patient, societal] were comparable to multiple imputed data, except for productivity losses [Supplementary Table S4, available as Supplementary data at *ECCO-JCC* online].

CD: current smokers were found to incur higher societal costs than never-smokers in CD, although not statistically significantly so (€10,261 [95% CI €7,852 – €12,690] in smokers vs €8,823 [€7,351 – €10,387] in never-smokers, $p = 0.36$; and €8,211 [€6,380 – €10,228] in ex-smokers, $p = 0.20$) [Table 3].

UC: smoking was not associated with societal higher costs (€ 3,641 [€1,954 – €5,624] in smokers vs €3,325 [€2,656 – €4,006] in never-smokers, $p = 0.78$; and €3,983 [€2,719 – €5,532] in ex-smokers, $p = 0.83$) [Table 3].

3.4. Effects of smoking cessation

Annual societal costs of IBD patients who quitted smoking more than5 years before inclusion were lower than those of patients who

Table 2. Multivariable analysis for 10% highest total costs in inflammatory bowel disease.

Characteristics	10% highest societal costs			10% highest healthcare costs		
	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	*p*-Value	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	*p*-Value
Current smoking [vs never-smoking]	1.97 [1.19 – 3.25]*	1.92 [1.14 – 3.24]	0.02	1.80 [1.10 – 2.93]*	1.38 [0.76 – 2.52]	0.29
Ex-smoking [vs never-smoking]	1.26 [0.80 – 1.88]	-	-	0.84 [0.54 – 1.31]	-	-
Female gender [vs male gender]	1.44 [0.98 – 2.12]*	1.09 [0.66 – 1.82]	0.62	1.68 [1.14 – 2.49]*	1.39 [0.77 – 2.50]	0.27
Low education [vs high education]	1.04 [0.71 – 1.53]	-	-	1.08 [0.73– 1.59]	-	-
Age [per year]	0.97 [0.95 – 0.98]*	0.96 [0.94 – 0.98]	< 0.01	0.97 [0.95 – 0.98]*	0.95 [0.93 – 0.98]	< 0.01
Disease duration [per year]	0.98 [0.96 – 1.00]*	1.00 [0.98 – 1.03]	0.89	0.99 [0.97 – 1.00]	-	-
Flare at baseline [vs remission at baseline]	3.06 [2.01 –4.67]*	3.08 [1.79 – 5.31]	< 0.01	2.79 [1.82 – 4.27]*	2.99 [1.63 – 5.49	< 0.01
Employed at baseline [vs unemployed at baseline]	0.73 [0.47 – 1.15]	-	-	0.52 [0.33 – 0.81]*	0.52 [0.29– 0.93]	0.08
Abdominal surgery in the past [vs no abdominal surgery in the past]	1.33 [0.91 – 1.96]	-	-	1.61 [1.10 – 2.36]*	1.63 [0.94 – 2.83]	0.08

OR, odds ratio; CI, confidence interval.
*Variables with a *p*-value < 0.10 at univariable analysis, age and gender were integrated in the multivariable model.

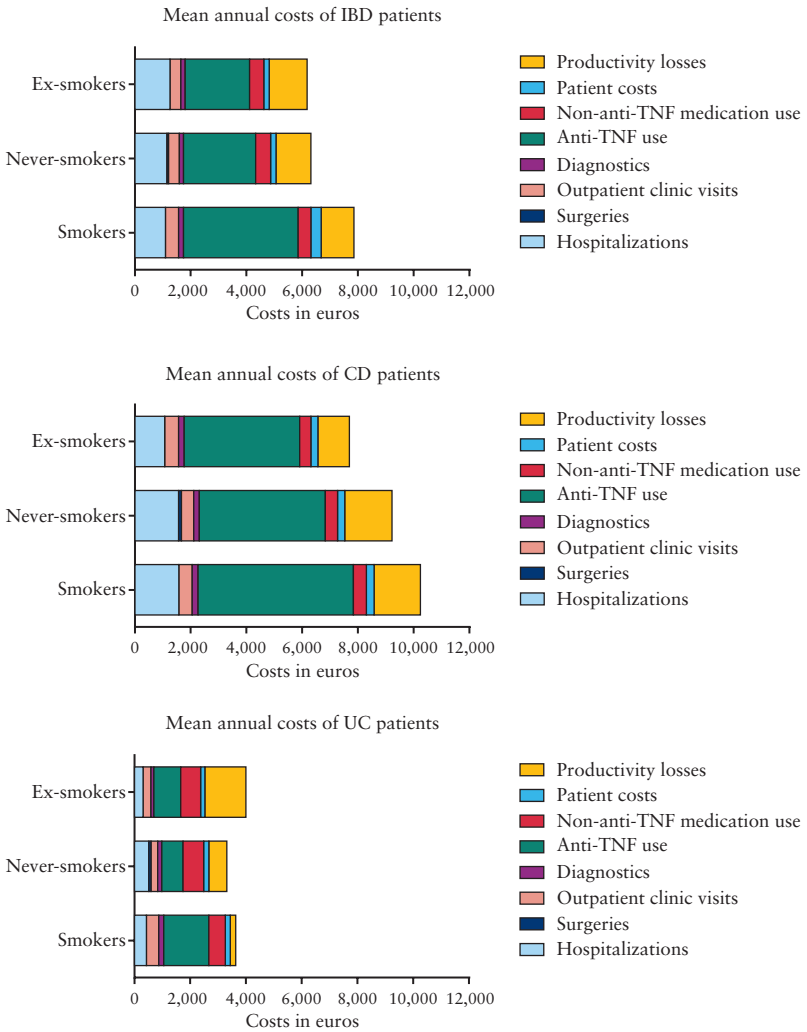

Figure 2. Mean annual costs of smokers, never-smokers and ex-smokers, expressed in 2014 euros.

quitted smoking within 5 years before inclusion (€5,135 [95% CI €4,122 – €6,303] vs €9,342 [€6,010 – €12,788], $p = 0.01$). This applied to patients with either CD or UC, although not statistically significantly so for the latter group [$p < 0.05$ and $p = 0.42$, respectively] [Supplementary Table S5, available as Supplementary data at *ECCO-JCC* online]. In CD patients who quitted smoking within

Table 3. Costs of smokers, never-smokers and ex-smokers in 2014 euros*

Mean + 95% CI	1.Current smokers	2.Never-smokers	3.Ex-smokers	*p*-Value[1 vs 2]	*p*-Value[1 vs 3]
IBD	*n* = 169	*n* = 638	*n* = 393		
Healthcare costs	6,381 [5,063 – 7,829]	4,573 [4,011 – 5,206]	4,163 [3,422 – 4,914]	0.01	< 0.01
Hospitalizations	1,119 [639– 1,653]	828 [613– 1,070]	798 [488 – 1,199]	0.31	0.36
Surgeries	18 [0 – 41]	54 [27 – 87]	18 [4 – 34]	0.25	1.00
Anti-TNF use	4,119 [3,074 – 5,215]	2,572 [2,088 – 3,056]	2,296 [1,737 – 2,860]	0.01	< 0.01
Other medication use	455 [416 – 490]	547 [51 – 581]	509 [451 –509]	0.03	0.21
Diagnostics	173 [126 – 222]	148 [128 – 169]	146 [120 – 177]	0.33	0.31
Outpatient clinic visits	449 [366 – 547]	381 [333 – 437]	374 [328 – 429]	0.23	0.13
Patient costs	355 [222 – 564]	208 [179 – 243]	192 [157 – 231]	0.02	0.03
Productivity losses	1,169 [453 – 2,091]	1,236 [816 – 1,747]	1,356 [741 – 2,065]	0.90	0.75
Societal costs	7,905 [6,234 – 9,864]	6,017 [5,186 – 6,946]	5,710 [4,687 – 6,878]	0.06	0.04
Crohn's disease	*n* = 114	*n* = 309	*n* = 169		
Healthcare costs	8,316 [6,402– 10,228]	6,870 [5,798 – 7,949]	6,840 [5,350 – 8,470]	0.19	0.24
Hospitalizations	1,514 [827– 2,317]	1,161 [766 – 1,572]	1,557 [835 – 2,491]	0.43	0.94
Surgeries	27 [3 – 59]	52 [19 – 89]	29 [2 – 61]	0.46	0.91
Anti-TNF use	5,571 [4,155 – 6,995]	4,503 [3,687 – 5,404]	4,119 [2,987 – 5,321]	0.23	0.13
Other medication use	470 [393 – 553]	461 [407 – 520]	441 [374 – 514]	0.87	0.61
Diagnostics	179 [123 – 241]	169 [139 – 198]	180 [136 – 229]	0.77	0.97
Outpatient clinic visits	494 [396 – 596]	474 [399 – 558]	483 [401 – 578]	0.81	0.89
Patient costs	292 [232 – 359]	232 [184 – 287]	229 [164 – 310]	0.21	0.26
Productivity losses	1,654 [675 – 2,794]	1,721 [951 – 2,585]	1,142 [519 – 1,937]	0.94	0.49
Societal costs	10,261 [7,852 – 12,690]	8,823 [7,351 – 10,387]	8,211 [6,380 – 10,228]	0.36	0.20
Ulcerative colitis	*n* = 38	*n* = 260	*n* = 165		
Healthcare costs	3,287 [1,644 – 5,143]	2,508 [2,000 – 3,007]	2,368 [1,673 – 3,180]	0.36	0.31
Hospitalizations	438 [0 – 1,176]	534 [314 – 777]	301 [101 – 551]	0.80	0.64
Surgeries	0 [0 – 0]	42 [2 – 92]	11 [0 – 33]	0.53	0.63
Anti-TNF use	1,611 [234 – 3,221]	765 [365 – 1,167]	941 [389 – 1,591]	0.20	0.39
Other medication use	595 [465 – 732]	757 [703 – 808]	735 [666 – 799]	0.04	0.08
Diagnostics	199 [128 – 279]	124 [96 – 154]	109 [80 – 144]	0.10	0.02
Outpatient clinic visits	418 [227 – 654]	261 [220 – 303]	264 [217 – 324]	0.04	0.06
Patient costs	176 [109 – 252]	175 [130 – 224]	149 [111 – 187]	0.97	0.57
Productivity losses	177 [0 – 497]	642 [347 – 950]	1,467 [587 – 2,568]	0.33	0.26
Societal costs	3,641 [1,954 – 5,624]	3,325 [2,656 – 4,006]	3,983 [2,719 – 5,532]	0.78	0.83
IBD-unknown	*n* = 17	*n* = 69	*n* = 59		
Healthcare costs	338 [167 – 496]	2,066 [1,133 – 3,158]	1,507 [776 – 2,438]	0.16	0.19
Patient costs	1,178 [83 – 3,264]	227 [142 – 317]	208 [144 – 287]	0.07	0.08
Productivity losses	135 [11 – 324]	1,300 [263 – 2,754]	1,659 [388 – 3,419]	0.46	0.40
Societal costs	1,639 [386 – 3,810]	3,591 [1,938 – 5,633]	3,374 [1,710 – 5,549]	0.38	0.41

CI, confidence interval; IBD, inflammatory bowel disease; TNF, tumour necrosis factor.
*In 2014, 1€ was equal to 0.754 US$, or 0.814 US$ when using data on purchasing power parity.[23]

5 years before inclusion, anti-TNF compounds were more frequently prescribed than in patients who quit smoking longer than 5 years previously [34.4% vs 19.1%, $p < 0.01$] [Supplementary Table S6, available as Supplementary data at *ECCO-JCC* online]. The post-hoc multivariable analysis revealed that an increasing number of years after smoking cessation was associated with a lower risk for high annual healthcare costs in ex-smoking IBD patients, adjusted for age, disease duration, gender and disease severity (adjusted OR 0.95 [95% CI 0.91- 0.99] per year, $p = 0.02$) [Table 4].

3.5. Employment rates

CD: current smokers were less frequently employed than never-smokers [57.3% vs 73.1%, $p < 0.01$] [Table 1], and more frequently partially incapacitated than never-smoking patients [21.6% vs 11.8%, $p < 0.01$]. Of the working CD population, never-smokers worked on average 1.8 h more per week than current smokers {32.7 (standard deviation [SD] 8.6) vs 30.9 (SD 9.5), $p = 0.04$}, whereas ex-smokers worked on average 2.3 h more than current smokers (33.2 [SD 9.8], $p = 0.04$).

UC: in UC, no differences were found in employment rates between smokers and never-smokers [Table 1]. However, smoking patients were more frequently partially incapacitated than never-smoking patients [18.9% vs 7.5%, $p < 0.01$], and ex-smoking patients [18.9% vs 8.9% $p = 0.01$]. Among the employed UC population, average working hours in never-smokers, smokers and ex-smokers were comparable (33.6 [SD 9.0] vs 33.1 [SD 9.9] and 32.7 [SD 9.6], respectively, overall $p = 0.56$).

3.6. Work, productivity and activity impairment

Measured over the preceding 7 days on one occasion during follow-up, CD patients who currently smoked had more often been absent from work due to IBD-related illness (9% [SD 24] vs 4.1% SD [14.7], $p = 0.04$) and reported higher IBD-related activity impairment than never-smokers [Figure 3, Supplementary Table S7, available as Supplementary data at *ECCO-JCC* online]. Furthermore in CD, current smokers reported a higher presenteeism, work and activity impairment than ex-smokers. In UC, current smokers reported higher work and activity impairment compared with never-smokers (work impairment 20.1 [SD 28.6] vs 12.1 [SD 17.8], $p = 0.04$), and higher activity impairment than both never-smokers and ex-smokers [Figure 3, Supplementary Table S7].

3.7. Health-related quality of,life

The HrQoL was lower in the smoking population than in either never-smokers or ex-smokers, which applied to both CD and UC, both measured using disease-related and generic instruments at baseline and during follow-up.

3.7.1. Disease-related HrQoL

Adjusted for demographic data and disease severity, current smoking was associated with the 10% lowest IBDQ scores as compared with never smoking, with an OR of 1.54 [95% CI 0.93–2.56, $p = 0.09$] in CD, and 1.55 [0.88 – 2.72, $p = 0.13$] in UC [Supplementary Table S8, available as Supplementary data at *ECCO-JCC* online]. Further specified, median IBDQscores of the total population at baseline were 170 [IQR 145 – 191] in smokers, vs 185 [161 – 202] in never-smokers [$p < 0.01$], and 179 [158 – 198] in ex-smokers [$p < 0.01$] [Figure 4; Supplementary Table S9, available as Supplementary data at *ECCO-JCC* online].

3.7.2. Generic HrQoL

Adjusted for demographic data and disease severity, current smoking was associated with the 10% lowest EQ-VAS scores as compared with never smoking with an OR of 2.18 [95% CI 1.33 – 3.58, $p < 0.01$] in CD, and 2.04 [0.94 – 4.41, $p = 0.07$] in UC [Supplementary Table S10, available as Supplementary data at ECCO-JCC online]. Current smoking was independently associated with the 10% lowest EQ indices as compared with never smoking, as well [Supplementary Table S10]. Further specified, in CD patients smoking was associated with more problems in all five dimensions of the EQ-5D-3L and resulted in lower EQ indices and lower EQ-VAS scores [Figure 4; Supplementary Table S10]. In UC, smoking was associated with more problems in all but the anxiety/depression dimension, and resulted in lower EQ indices and EQ-VAS scores.

3.7.3. Ex-smokers

For both CD and UC patients, the HrQoL did not differ between patients who quitted smoking within and more than 5 years prior to inclusion, independent of the instruments used [Supplementary Table S11, available as Supplementary data at *ECCO-JCC* online].

4. Discussion

In this large, prospective multicentre cohort study of over 3000 IBD patients, we found that smoking was associated with substantial higher annual IBD-related societal and healthcare costs,

Table 4. Multivariate analysis for the 10% highest costs in the ex-smoking IBD population.

Characteristics	10% highest annual societal costs			10% highest annual healthcare costs		
	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	*p*-Value	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	*p*-Value
Number of years after smoking cessation [per year]	0.96 [0.93 – 0.99]	0.96 [0.91 – 1.00]	0.06	0.95 [0.92 – 0.99]	0.95 [0.91 – 0.99]	0.02
Female gender [vs male gender]	1.34 [0.71 – 2.65]	1.09 [0.53 – 2.23]	0.82	1.37 [0.71 – 2.65]	1.03 [0.50 – 2.11]	0.95
Low education [vs high education]	2.03 [0.94 – 4.41]	2.00 [0.90 – 4.46]	0.09	2.03 [0.94 – 4.41]	2.00 [0.90 – 4.49]	0.09
Age [per year]	0.97 [0.94 – 0.99]	0.98 [0.95 – 1.02]	0.35	0.96 [0.94 – 0.99]	0.98 [0.94 – 1.01]	0.20
Disease duration [per year]	0.99 [0.96 – 1.02]	1.01 [0.97 – 1.04]	0.69	1.00 [0.97 – 1.03]	1.02 [0.99 – 1.06]	0.17
Flare at baseline [vs remission at baseline]	3.18 [1.55 – 6.51]	3.19 [1.51 – 6.77]	< 0.01	3.18 [1.55 – 6.51]	3.27 [1.53 – 6.99]	< 0.01
Employed at baseline [vs unemployed at baseline]	0.76 [0.33 – 1.71]	-	-	0.56 [0.25 – 1.27]	-	-
Abdominal surgery in the past [vs no abdominal surgery in the past]	1.10 [0.60 – 2.18]	-	-	1.40 [0.72 – 2.73]	-	-

Factors with a *p*-value < 0.10 in the univariable analyses, age, gender and disease duration were incorporated in the multivariable analyses.
Purchasing power parity is used to avoid the effects of the different levels of prices within a group of countries at a point in time.
CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio.

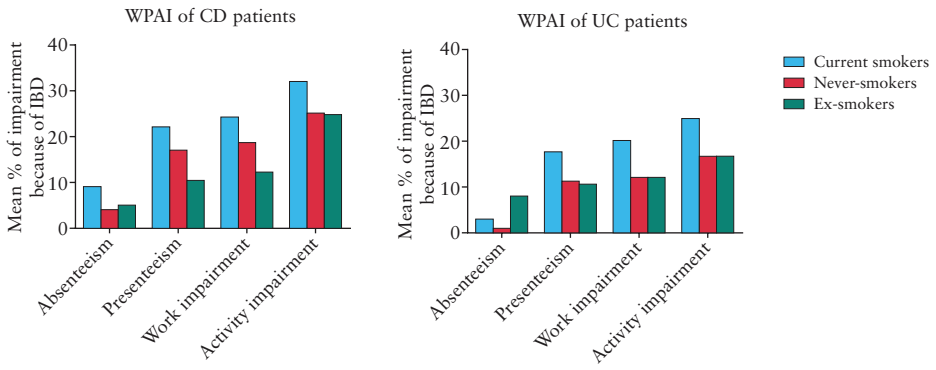

Figure 3. Percentages of impairment in work productivity and daily activities because of IBD of smokers, neversmokers and ex-smokers.

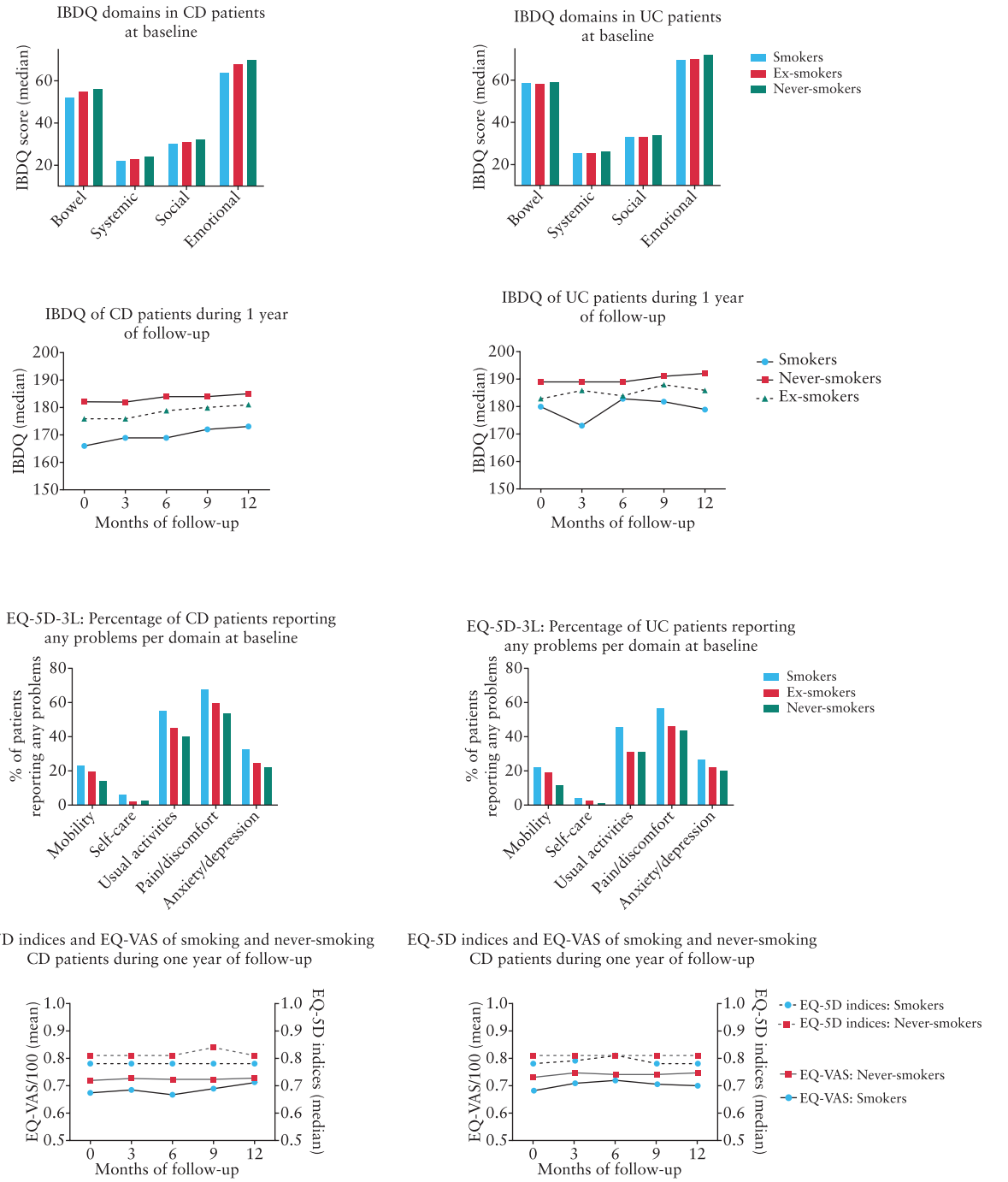

Figure 4. The Health-related quality of life of smoking, never-smoking and ex-smoking IBD patientsl. EQ-5D indices and EQ-VAS of ex-smokers can be found in table s.11. Scores ranged between those of smokers and never-smokers.

predominantly driven by a higher use of anti-TNF compounds. Moreover, we found that the annual societal costs of patients who quitted smoking within 5 years before inclusion were higher than the annual societal costs of those who quitted more than 5 years previously. In both CD and UC, smokers reported a lower HrQoL than never-smokers, measured by both generic and disease-specific instruments.

Although the impact of smoking has been found to represent a substantial burden on national health services from a public health perspective,[30–33] the economic impact of smoking in IBD or other chronic inflammatory conditions has never been evaluated. In our study, annual IBD-related societal costs were 31% higher among smokers compared with patients who never smoked. This association was found to be independent of demographic characteristics and disease severity. The majority of these societal costs were driven by healthcare costs. CD patients are more likely to smoke than UC patients,[34] and smoking has a well-established negative effect on the course of CD.[5–7] The economic impact of smoking in IBD was therefore mainly determined by a higher consumption of healthcare in smoking CD patients. Specifically, we observed a higher prescription rate of anti-TNF compounds in smoking CD patients. We expected the societal costs of non-smoking UC patients to be higher than

those of current smokers. However, costs did not differ significantly between these groups. Therefore, the presented societal costs of IBD patients represent the total economic impact of smoking among the whole IBD population, including CD, UC and IBD-unclassified patients. The incidence of smoking among the 1200 patients of whom annual costs were analysed, was slightly lower compared with the smoking incidence of the total initial patient population [n = 3030]. Since smoking was associated with higher costs, both healthcare and total costs may have been underestimated. However, a cost comparison with multiple imputed data showed no differences in cost outcomes.

Anti-TNF compounds are the main driver for increased healthcare costs in smokers. The most obvious explanation would be that this is the result of a 'smoking-increased disease severity-anti-TNF sequence'. Since smoking is one of the established risk factors for rapid progression and disability in CD,[5–7] it is also conceivable that treating physicians prescribe anti-TNF compounds in these patients in the context of progressive therapeutic decision making, irrespective of disease severity.

CD patients who quit smoking more than 5 years before inclusion had substantially lower societal costs than those who quit more recently [$p < 0.05$]. This was mainly due to a lower use of anti-TNF compounds [$p < 0.01$]. In the multivariate analysis, we observed that the number of years after smoking cessation was significantly associated with a reduced risk for high costs, adjusted for disease duration. These results suggest that the negative effects of smoking on the disease course of CD diminish over time following smoking cessation.[35] This association may be [partially] caused by increased anti-TNF prescription rates over the past few years as well, as observed in our and other cohorts.[36–38] In UC patients, costs of patients who quit smoking longer ago were also lower, but in these patients this was mainly caused by lower productivity losses. The lack of statistical significance in these patients can probably be attributed to a type II error. Obviously, we cannot infer a causal relationship between smoking and costs based on our results, because of the possibility of residual confounding. Smoking behaviour may be a proxy for an unhealthy lifestyle, such as a poor diet or a lack of physical activity. However, the finding that annual societal costs were considerably lower in patients who quit smoking longer ago provided additional support for causality. Recently, an economic evaluation for funding a smoking cessation programme for CD patients, using a Markov model, was published. [39] The perspective was the publicly funded healthcare system. All strategies [ie counselling, nicotine replacement therapy, nicotine replacement therapy + counselling, and Varenicline] were dominant [cost saving] over a strategy with no programme. The economic consequences of smoking in CD, as presented in our study, underscore this need for smoking cessation programmes. In clinical practice, a successful smoking cessation programme should include a multifaceted approach, aimed to raise awareness, educate, manage physical addiction and focus on the social context of smoking.[40]

Counterintuitively, productivity losses appeared to be slightly, but not statistically significantly, higher in ex-smokers and never-smokers than in current smokers. These outcomes might have resulted from the fact that productivity losses were calculated by a formula including gender, age, number of absent days and number of hours worked per day. In this formula, higher salary rates were applied for increasing age and for men compared with women.[22] In our study, smoking participants were more often unemployed or partially incapacitated, worked fewer hours per week, were more often female and were younger. We speculate that this imbalance explains the slightly lower productivity losses found in smoking IBD patients. Since work and activity impairment was measured with IBD-specific tools, it is likely that productivity losses can be attributed to IBD-related causes.

Smoking was found to be a strong predictor for lower disease-specific and generic HrQoL scores, both in CD and in UC patients, even after correction for known influencing factors for HrQoL.[41,42] As expected, the effect of smoking on HrQoL was most pronounced in CD. Nonetheless, smoking was not independently associated with the lowest 10% of IBDQ scores in our study, although its detrimental effect on the course of disease in CD is well known.[5–7] Here, disease activity could have served as a collider for lower HrQoL scores in smoking CD patients.[43] The employment of several tools for assessment of HrQoL corroborated our conclusion that smoking worsened the HrQoL in both CD and UC patients.

The strengths of our study included: the size of our cohort, representing the whole IBD population as being derived from both academic and non-academic centres; the prospective nature of data collection; and the fact that all relevant costs [healthcare costs, patient costs and productivity losses] were taken into account. However, self-report as a method to calculate the incurred costs has to be considered a limitation of this study. Patients may under-report or exaggerate their consumption of healthcare. We recently reported that self-reported healthcare utilization in IBD patients is highly concordant with administrative data, however.[44] Therefore we expect the current data to reliably reflect consumption of healthcare. Furthermore, as smoking behaviour was only recorded at baseline, we were not able to make allowances for patients who started or quit smoking during follow-up. Since smoking behaviour has been shown to be rather constant over a relatively short period of time,[22,45] and fluctuations in smoking behaviour are likely to be balanced by the large size of our cohort, outcomes will not have been meaningfully altered by this constraint. Although smoking was associated with substantial higher costs in CD patients, the differences in societal costs did not reach a statistically significant p-value of < 0.05. It can be argued that these cost differences are clinically relevant, however. Because of the broad inclusion criteria in cohort studies, study populations are more heterogeneous compared with randomized trials, which impacts on confidence intervals of the outcomes. Hence, the application of strict p-values in observational cohort studies can be questioned.[46] Moreover, outcomes in CD were fairly consistent, since smoking was found to have negative effects on the disease course, societal costs, IBD-related quality of life, generic quality of life and work productivity. Also, smoking cessation was accompanied by a drop in societal costs, consistent with lower consumption of health care.

In the interpretation of the economic impact of smoking in IBD, concerns may arise regarding the representativeness of calculated costs. For example, selection bias may have been introduced by the fact that not all patients who were invited to participate in the COIN-study responded.[2] Our non-responder-study revealed no relevant differences between responders and non-responders regarding demographic data and disease course variables, however.[2] Second, the response rate in the COIN-study after 1 year of follow-up was 60% in CD and 66% in UC patients,[47] and complete cost data of all questionnaires during this 1 year period were available in 1200 of 3030 initial patients. In a comparison between patients who completed all follow-up questionnaires in the COIN study and patients who were lost to follow-up, responders were older and had longer disease duration.[47] Since older age was associated with lower costs in this cohort, total costs may have been underestimated. However, presented costs in our study were comparable to costs calculated

by multiple imputation, which made it unlikely that missing data in this cohort caused major underestimation or exaggeration of true incurred costs. As participants were derived from 14 different hospitals, and the disease duration at inclusion of study participants ranged widely from 9 months to 73 years, we believe that our results truly reflected societal costs in an average IBD population. Even though healthcare costs differ to a large extent between countries, comparable impacts of smoking on healthcare costs in European countries and the USA may be anticipated. We opted for a time frame of 1 year because of the good clinical interpretability of annual costs. As the costs of smokers after 1 year of follow-up were already considerably higher than those of non-smokers, it is likely that the full economic impact of smoking, measured over a longer period of time, will be even more important.

Smoking induces a spectrum of negative health effects in the general population, and is known to have deleterious effects on the course of CD. In the present study, it is clearly demonstrated that smoking is associated with a lower HrQoL in both CD and UC patients. Most importantly, smoking entails a substantial economic burden to the healthcare system, which necessitates an active approach to achieve smoking cessation.

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Conflict of Interest

MS has no competing interests. MJJM has no competing interests. MEvdV has no competing interests. HHF has acted as a consultant for AbbVie. GD participated on an advisory board of Mundipharma. AAvB has acted as a consultant for AbVvie, Ferring, MSD-Merck and Tramedico, and received payments for lectures from AbbVie, Ferring, Pfizer and Takeda. DdJ has acted as a consultant for Synthon Netherlands and received payments for lectures from AbbVie, Ferring and MSD. JvdW has acted as a consultant for AbbVie, Ferring, Shire and MSD and received payment for lectures from AbbVie, Falk Pharma and MSD. MRC has no competing interests. CC has no competing interests. JM has acted as a consultant for AbVvie, MSD, Ferring and Falk and received payments for lectures for AbbVie and MSD. PvdM received payments for lectures for Falk. NM has no competing interests. CYP has acted as a consultant for AbbVie and received payments for lectures from Ferring and MSD. RV has no competing interests. AvdM has acted as consultant for AbbVie, MSD, Ferring and Falk and received payments for lectures from AbbVie and MSD. MP has no competing interests. PDS has no competing interests. BO has acted as a consultant for AbbVie, Takeda and MSD and received payment for lectures from Ferring, MSD and AbbVie.

Author Contributions

Study concept and design: MS, BO, MJJM. Acquisition of data: MS, BO, MJJM, MEvdV. Interpretation of data: MS, BO, MJJM. Drafting of manuscript: MS. Critical revision of the manuscript: all authors. Final approval of the submitted manuscript: all authors.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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