Societal and economic aspects of inflammatory bowel diseases

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Societal and economic aspects of inflammatory bowel diseases

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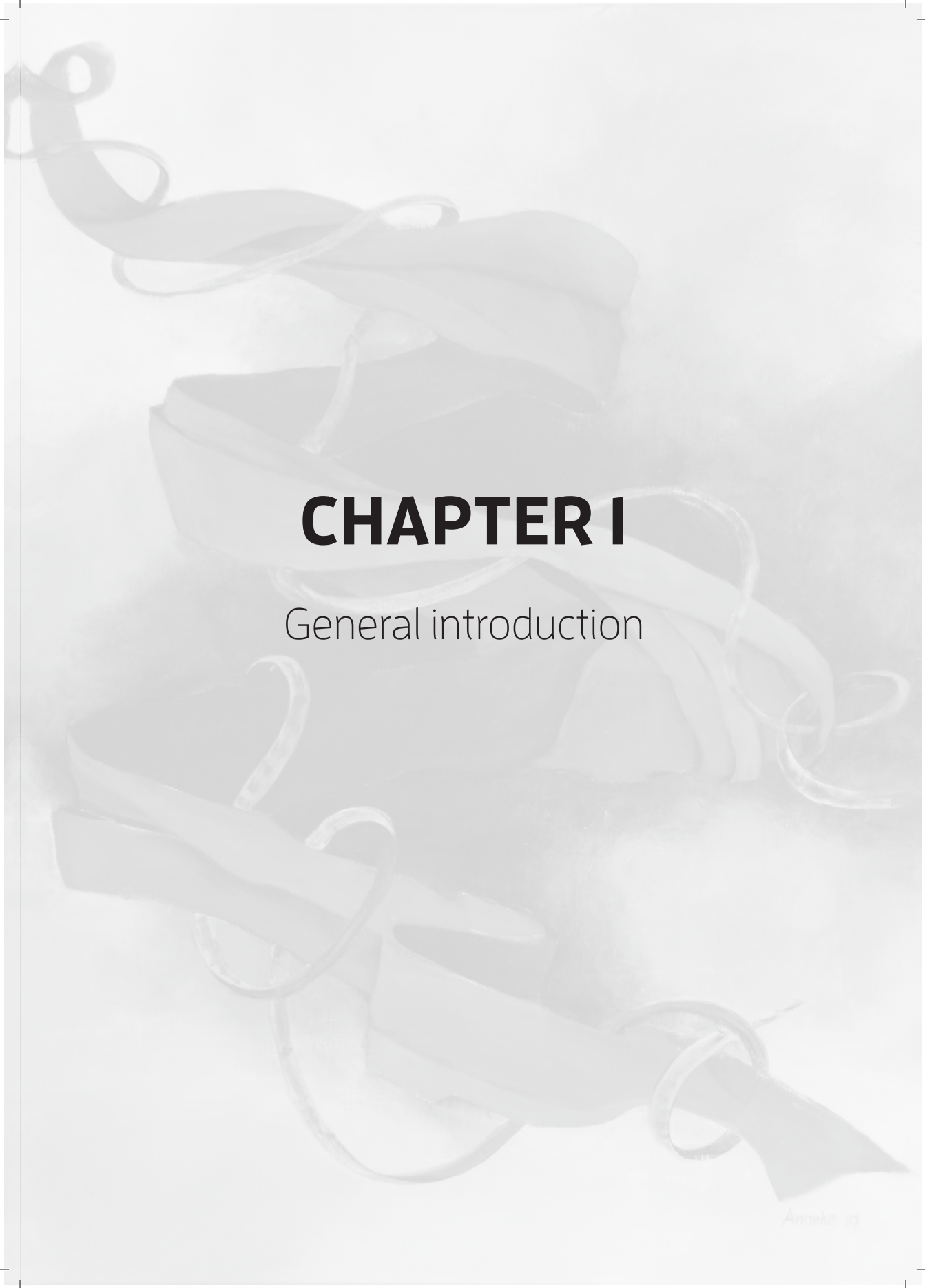

CHAPTER I

General introduction

1.1 General introduction

Inflammatory bowel diseases

Inflammatory Bowel Diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC) are a chronic inflammatory diseases primarily affecting the gut. The exact cause of IBD is unknown, but both genetic and environmental factors are thought to be involved. [1,2] Currently, over one million residents in the United States of America and 2.5 million residents in Europe are estimated to suffer from IBD.[3] IBD is predominantly diagnosed in the second or third decade of life.[4] Reportedly, the prevalence of UC and CD is the highest in developed countries, but the incidence is rising in previously low-incidence areas such as Asia and Eastern Europe.[5] In the Netherlands alone, the number of Dutch adult IBD patients in 2014 was estimated to be approximately 85,000.[6] The natural course of IBD is characterized by flares, interspersed with periods of remissions. IBD is frequently accompanied by extra-intestinal manifestations, involving predominantly the joints, the skin and the eyes.[7] Many patients receive long-term therapy aimed at maintaining remission, and thereby preventing disease progression, complications, such as stricturing or penetrating disease and averting gastro-intestinal surgery.[8,9] In spite of the recent introduction of biologicals,[10] IBD cannot be cured and therefore, surgery is still an indispensable part of the treatment algorithm in these patients.

Burden of disease

Costs - IBD has disabling effects on the lives of patients.[8] IBD affects physical health, psychological health, (work) productivity and health-related quality-of-life (HrQoL). The economic burden of IBD is substantial, resulting from significant healthcare costs, patient costs and productivity losses.[4,11]

Work - IBD considerably impacts work-related outcomes.[12] When compared to age-and sex-matched controls, employment is lower in IBD patients[13] and patients with disease-symptoms are more than two times as likely as the non-IBD population to be out of the labour force.[14] Moreover, both CD and UC patients are reported to have a higher frequency of work disability than comparator groups.[13,15]

Quality-of-life - The HrQoL fluctuates in IBD patients, and is negatively influenced by relapses and hospitalizations, whereas patients in long-term remission are thought to have comparable HrQoL with the general population.[16–18] Conversely, biological treatment is associated with improved HrQoL.[16] Perceptions about the illness can have a significant impact on the HrQoL.[19,20]

COIN study (chapter 2)

In general, costs of healthcare are substantial and still increasing year by year.[21] Chronic diseases drive a significant portion of healthcare costs.[22] The 'Costs of Inflammatory Bowel Disease In the Netherlands study' (COIN study) was initiated in 2011 with the aim to study the disease-related costs and HrQoL of patients with IBD.[23] All IBD patients from seven University Medical Centres and seven General Hospitals aged 18 years or older were eligible for inclusion. Patients were invited to fill-out a baseline questionnaire on demographics, disease phenotype, disease severity and HrQoL, followed by three-monthly questionnaires collected for 2.5 years, on demographics, disease course items, healthcare utilization and HrQoL. Finally, 3,030 IBD patients participated in the study.

A preceding thesis, based on the COIN study, was aimed at calculating the costs of IBD in current clinical practice ("*Costs of Inflammatory Bowel Disease in the Netherlands: the COIN study, by Mirthe van der Valk*"). One of the main findings of this thesis was that healthcare costs of IBD have shifted from hospitalizations towards anti-TNF therapy.[23] However, total healthcare expenditure remained constant. Average IBD-specific healthcare costs in 2011 were estimated at €6,500 per year for CD patients and €2,380 for UC patients.

In the current thesis, we corroborate these previous findings and explore the changes of societal costs for IBD in the Netherlands from the years 2011 until 2013. Moreover, we assessed the validity of self-reported healthcare utilization of IBD patients over the past year.

Influence of smoking on the course and costs of Inflammatory Bowel Diseases (chapter 3)

In addition to medical therapy, the HrQoL and course of disease can be influenced by patient behaviour, most notably by smoking. Smoking affects the course of disease in CD and UC differently, having a negative effect on the course of CD and a beneficial effect in UC.[24–26] Furthermore, smoking cessation has been reported to have positive effects on the course of CD.[27] The association between smoking and extra-intestinal manifestations, and the impact of smoking on HrQoL and costs have currently not been investigated thoroughly.

Influence of medication adherence on the course and costs of Inflammatory Bowel Diseases (chapter 4)

Adherence to medication is a crucial component of patient care, and is indispensable for reaching clinical goals. Complete adherence, however, is difficult to achieve in a chronic condition like IBD. Non-adherence is reportedly associated with increased disease activity, loss of response to therapy and even increased cost of healthcare in patients with CD or

UC.[28] The heterogeneity of these studies with respect to the definition of adherence and associated outcomes, leave many remaining questions, however.

Introduction of biosimilars (chapter 5)

Biosimilars are copy versions of licenced biological agents, which are developed after patents of original agents expire. In 2015, Remicade® came off patent, and biosimilars of infliximab entered the market.[32] Biosimilars are known to be cheaper than their originators, and offer competition to some of the most expensive drugs on the market. Large cost savings in the field of IBD are therefore expected. In this last chapter, we simulate the introduction of biosimilars for infliximab in the Netherlands and calculated associated IBD related cost savings for in the near future.

1.2 Aims of this thesis

IBD is a chronic disorder with disabling effects on the lives of patients, resulting in a high economic burden to society. The prospectively collected data of the COIN study enabled us to gain new insights into several societal and economic aspects of IBD. In this thesis, we addressed the following questions:

Chapter 2: How can we measure healthcare costs of Inflammatory Bowel Disease patients and how have these costs evolved over the last few years?

Chapter 3: What is the impact of smoking on extra-intestinal manifestations, disease-related costs and quality-of-life of Inflammatory Bowel Disease patients?

Chapter 4: How can non-adherence to medical therapy in Inflammatory Bowel Disease be assessed; which factors can predict future non-adherence and what is the impact of non-adherence on the disease course, costs and quality-of-life of patients?

Chapter 5: What is the current and future economic impact of the introduction of biosimilars in Inflammatory Bowel Disease?

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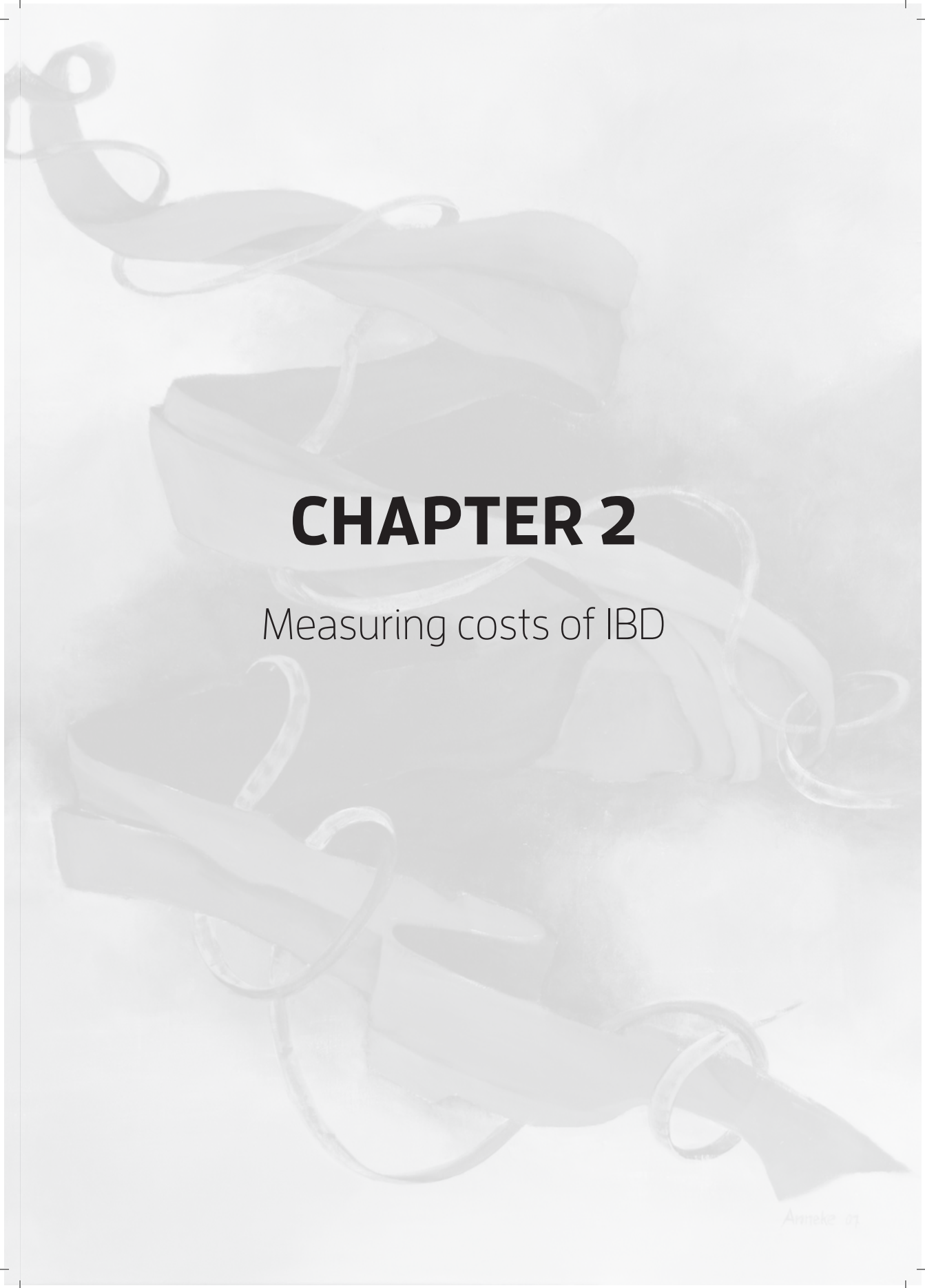

CHAPTER 2

Measuring costs of IBD

CHAPTER 2.I

Self-reported healthcare utilization of inflammatory bowel disease patients correlates perfectly with medical records

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ABSTRACT

Background: Studies on the costs of health care in patients with inflammatory bowel disease (IBD) are increasingly conducted through the collection of self-reported data. We aimed to assess the concordance between estimated annual costs based on self-reported health care utilization and administrative data in IBD.

Methods: Consecutive patients with Crohn's disease or ulcerative colitis visiting the outpatient clinic were enrolled. Participants were asked to fill out a questionnaire on their IBD-specific health care utilization over the past year. Registered health care utilization over the same time period was extracted from medical records. Health care resources were multiplied by their unit prices to obtain costs. Cost estimates were compared, and correlation, sensitivity, and specificity were calculated.

Results: In total, 101 patients (70 Crohn's disease, 31 ulcerative colitis) were enrolled. Mean direct health care costs were €4758 per year according to self-reported data and €4866 according to administrative data (r= 0.97). Hospitalizations and diagnostics were relatively underreported with a sensitivity of 75% and 88%, and a specificity of 100% and 88%, respectively. One of 7 surgical procedures was overreported, and only 1 of 25 patients did not report the use of anti–tumor necrosis factor compounds. Suffering from a flare or having a pouch predicted a decreased recall with an adjusted odds ratio of 3.5 (95% confidence interval, 1.3–9.6) and 10.7 (95% confidence interval, 1.1–107.6), respectively.

Conclusions: We report a high concordance between costs of self-reported health care utilization and administrative data over the past year in IBD. Self-reported health care utilization reliably measures the consumption of health care in IBD.

INTRODUCTION

The course of inflammatory bowel disease (IBD) is characterized by episodic flares on a background of chronic inflammation, frequently resulting in hospitalizations, surgeries, and the need for expensive medications such as anti–tumor necrosis factor (TNF) compounds.[1,2] In the current era of escalating health care costs and growing constraints on health care budgets, studies analyzing the costs of IBD are indispensable. Recently, several studies have been published on the costs of different chronic conditions, based on the collection of self-reported health care utilization.[2–4] This method allows for homogeneous data collection from large cohorts, but it may be questioned to what extent self-reported data accurately reflect the actual consumed health care and associated costs.

Self-reported health care utilization has been compared with administrative data in patients with osteoarthritis,[5] mental illness,[6] HIV,[7]and diabetes.[4,8] Longobardi et al[9] performed the only study in IBD on this topic. The generalizability of the results of this study was limited; however, because utilization data on major cost drivers such as diagnostic procedures, the use of anti- TNF compounds and surgeries were not included in the analysis. Moreover, the accuracy of self-reported costs of IBD-specific health care consumption has not been examined to date.

In this study, we aimed to assess the concordance between costs of self-reported health care utilization and administrative data over the past year in IBD.

MATERIALS AND METHODS

Ethical considerations

This study was locally approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

Patients

Consecutive patients with Crohn's disease (CD) and ulcerative colitis (UC) visiting the outpatient clinic of our clinic were approached for study participation between September 2014 and February 2015. All patients were taking part in the Parelsnoer IBD biobank study, a collaboration between all 8 Dutch university medical centers, initiated in 2007.[10] Patients aged 18 years or older were eligible for inclusion. After obtaining informed consent, participants were asked to fill out a written questionnaire on IBD-specific health care utilization over the year before their out- patient clinic visit (see supplementary Table 1). Included in the questionnaire were hospitalizations (including number of admissions and associated overnight stays), abdominal surgeries, diagnostic procedures (i.e., magnetic resonance scans, computed tomography scans, and colonoscopies), and the use of anti-TNF compounds (i.e., infliximab or adalimumab). In a previous study, the combination of these items accounted for the majority of total direct health care costs in IBD (CD 86.2%, UC 60.6%).[2] While entering data on self-reported health care utilization into a database, researchers were blinded for data in the electronic records of study participants. Subsequently, the health care utilization over the past 12 months was extracted from the electronic patient record of all patients and combined with the self-reported health care utilization database, using study numbers. Both self-reported and registered health care resources were multiplied by their unit prices to obtain direct health care costs (see supplementary Table 2). Current average unit prices, as published in the Dutch economic guidelines, were used for hospital admissions (including costs for overnight stays in the hospital, care of a medical specialist, and costs for nursing, medication, used materials, and overhead).[11] Average medication prices were obtained from the Dutch Healthcare Insurance Board.[12] Unit prices for surgeries and diagnostic procedures were extracted from the Dutch health authority, using the most appropriated Diagnosis Treatment Combination.[13] The price for a colonoscopy included the possibility for taking biopsies and polyp removal.

Statistical analysis

Baseline characteristics were analyzed using standard descriptive statistics. The self-reported data regarding health care utilization was linked to the administrative data to assess concordance by means of linear regression analysis. Mean total health care costs, all separate categories (hospitalizations, surgeries, diagnostic procedures, and the use of anti-TNF compounds), and both the 50% lowest and highest cost utilizers were compared between self-report and the medical records by an independent T-test. Sensitivity and specificity of self- reported items were calculated by a comparison with those registered in the medical records. Predictors for a decreased recall (defined as overreporting or underreporting of health care utilization according to medical records) were analyzed with univariable and multivariate logistic regression analysis. Both demographic predictors (gender, age, smoking status, education, and employment) and disease characteristics (flares, fistulas, pouches, preceding abdominal surgery, medication use, comorbidity, and type of IBD) were included in the analysis. Multivariable analysis was performed with covariables with a P value < 0.20 on univariable analysis. P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS Version 21 (Armonk, NY).

RESULTS

Patients

The questionnaire was presented to 108 patients. Two patients directly rejected participation. A total of 101 patients responded, yielding a response rate of 95%. Thirty (30.7%) patients had a diagnosis of UC; 70 (69.3%) had CD. Baseline characteristics of patients are shown in Table 1.

Concordance Between Costs of Self-report Compared with Administrative Health Care Utilization Data

The mean annual total direct health care costs of patients with IBD were €4758 (95% confidence interval [CI], €3182–€6334) according to self-report, and €4866 (95% CI, €3290–€6443) according to registered data, which was found to be highly correlated in both CD and UC (total IBD population: r = 0.97 [95% CI, 0.96–0.98], CD: r = 0.97 [95% CI, 0.95–0.98], UC: r = 0.99 [95% CI, 0.98–1.00]) (Fig. 1). Self-reported data were correlated with administrative data in both patients with low and high total annual direct health care costs (r = 0.65 [95% CI, 0.49–0.77] and r = 0.92 [95% CI, 0.85–0.96]), respectively. All separate components (hospitalizations, surgeries, diagnostics, and the use of anti-TNF compounds) were highly concordant between self- reported and administrative data as well (Fig. 2).

Sensitivity and Specificity of Self-reported Health Care Utilization

Regarding hospitalizations, patients were found to relatively underreport the number of hospital admissions, but slightly overreport the number of hospitalization days per reported admission, resulting in highly comparable mean costs per patient (Fig. 2; Tables 2 and 3). Surgical procedures over the past year were correctly recalled by all patients. However, 1 patient reported 2 surgeries over the past year, whereas only 1 surgical procedure was registered in the medical record. Moreover, patients slightly underreported the number of computed tomography scans (16 versus 17) and magnetic resonance scans (15 versus 16). One patient failed to report a colonoscopy, which was compensated by an overreporting of 1 colonoscopy by another patient. This resulted in an 88% sensitivity and 84% specificity for all diagnostic procedures. One of 25 patients did not report the use of anti-TNF compounds over the past year, which resulted in an underestimation of €18,760 for the total health care costs of this patient, and a mean underestimation of €130 per patient for the total study population.

Table 1. Baseline characteristics

Characteristics	IBD (n = 101)	CD (n = 70)	UC (n = 31)
Male gender (n, %)	48 (47.5)	30 (42.9)	18 (48.1)
Age – years (mean, SD)	52.7 (15.1)	51.9 (15.3)	54.6 (14.6)
Disease duration – years (median, IQR)	20.2 (13.2 – 33.2)	20.2 (13.2 – 32.2)	20.2 (12.5 – 32.2)
Smoking (n, %)			
Current	11 (10.9)	10 (14.3)	1 (3.2)
Never	51 (55.5)	33 (47.1)	18 (58.1)
Ex-smoker	37 (38.6)	27 (38.6)	12 (38.7)
Disease currently in remission (n, %)	75 (74.3)	51 (72.9)	24 (77.4)
Suffered from a flare during the past 12 months (n, %)	30 (29.7)	21 (30.0)	9 (29.0)
Stoma (n, %)	11 (10.9)	8 (2.9)	3 (9.7)
Pouch (n, %)	5 (5.0)	2 (2.9)	3 (9.7)
Fistula (n, %)	22 (21.8)	19 (27.1)	3 (9.7)
Abdominal surgery in the past (n, %)	21 (20.8)	17 (24.3)	4 (12.9)
Currently employed (n, %)	53 (52.5)	33 (47.1)	20 (64.5)
Current medication use (n, %)			
5-ASA	18 (17.8)	7 (10.0)	11 (35.5)
Steroids	4 (4.0)	3 (4.3)	1 (3.2)
Immunosuppressive drugs (Aza/6MP/MTX)	25 (24.8)	19 (27.1)	6 (19.4)
Anti-TNF	15 (14.9)	14 (20.0)	1 (3.2)
None	39 (39.8)	27 (38.6)	12 (38.7)
Comorbidity			
Diabetes	4 (4.0)	3 (4.3)	1 (3.2)
Cardiovascular disease	18 (17.8)	12 (17.2)	6 (16.1)
Malignancies	1(1.0)	1 (1.4)	0 (0.0)
Psychiatric disease	7 (6.9)	6 (8.5)	1 (3.2)
Rheumatic disease	23 (22.7)	18 (25.7)	5 (16.2)
Renal disease	3 (3.0)	2 (2.9)	1 (3.2)
Liver disease	1 (1.0)	0 (0.0)	1 (3.2)
Low education (n, %)	59 (58.4)	43 (61.4)	16 (51.6)

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; SD: standard deviation; IQR: interquartile range; 5-ASA: 5-aminosalicylic acid; Aza: azathioprine; 6MP: 6-mercaptopurine; MTX: methotrexate, Anti-TNF: anti-tumor-necrosis-factor

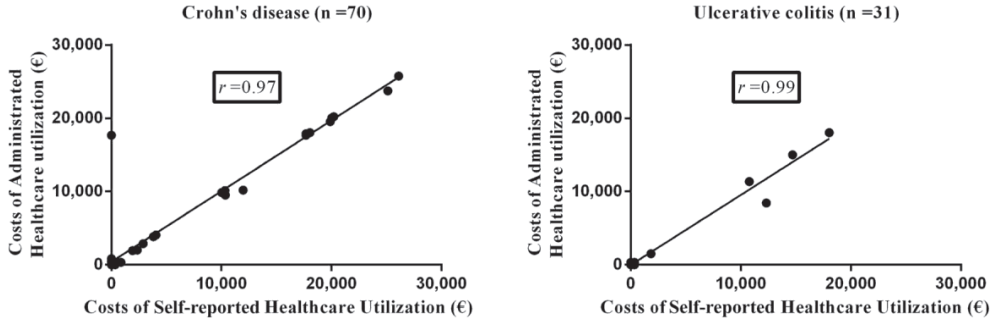

Fig.1: Correlation between total annual costs of self-reported health care utilization and administrative data of patients with IBD. Costs are given per individual patient, in Euros for the year 2014.

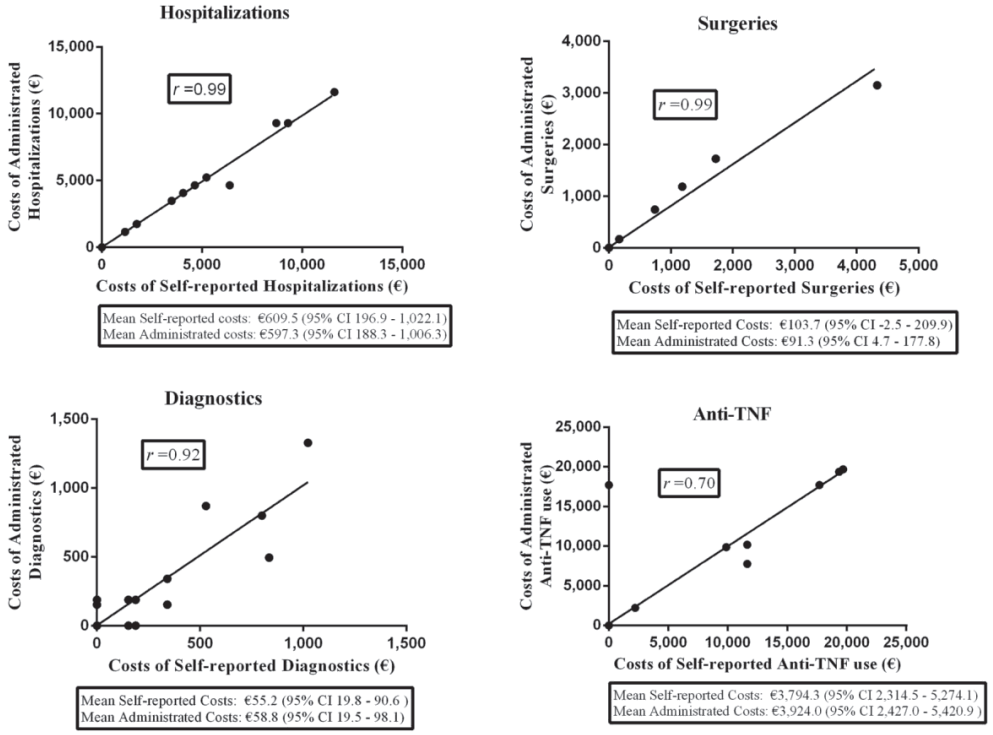

Fig.2: Correlation between annual costs of self-reported units and administrative data for hospitalizations, surgeries, diagnostics, and anti-TNF compounds in patients with IBD. Costs are given per individual patient, in Euros for the year 2014.

Predictors for a Poor Recall

Multivariate analysis revealed a current flare and the presence of a pouch as independent predictors for a decreased recall (adjusted odds ratio 3.5 [95% CI, 1.3–9.6] and 10.7 [95% CI, 1.1–107.6], respectively) (see supplementary Table 3). These patients both underreported and overreported the consumed health care of the previous year.

Table 2a. Concordance of self-report compared to administrative data – Units

Total number of units of healthcare consumption	Self-report (n)	Medical record (n)	Statistical comparison (Concordance)	Sensitivity/ Specificity (%)
Hospital admissions	12	16	75%	75/100
Hospitalization days	100	98	102%	
Surgeries	7	6	100%	100/99
Diagnostics				
CT-scans	16	17	94%	78/70
MR-scans	15	16	94%	
Colonoscopies	54	54	100%	
Anti-TNF use (total)				
Infliximab	7	7	100%	92/99
Adalimumab	17	18	94%	

CT: Computertomography; MR: Magnetic Resonance; TNF: Tumor necrosis factor

Table 2b. Concordance of self-report compared to administrative data – Patients

Total number of patients consuming units of healthcare	Self-reported (n,%)	Medical records (n,%)	Statistical comparison (Concordance)	Sensitivity/ Specificity (%)
Hospital admission	11 (10.9)	14 (13.9)	78.6%	79/100
Surgery	6 (5.9)	6 (5.9)	100%	100/100
Diagnostics				
CT-scan	9 (8.9)	8 (7.9)	113%	88/84
MR-scan	11 (10.9)	12 (11.9)	92%	
Colonoscopy	47 (46.5)	48 (47.5)	98%	
Anti-TNF use (total)				
Infliximab	7 (6.9)	7 (6.9)	100%	92/99
Adalimumab	17 (16.8)	18 (17.8)	94%	

CT: Computertomography; MR: Magnetic Resonance; TNF: Tumor necrosis factor

DISCUSSION

This cross-sectional cohort study among 101 patients with IBD shows a high concordance between the total costs of self- reported health care utilization and administrative data over the past year. We therefore conclude that, using a recall period of 1 year, self-report is an accurate tool to measure the majority of incurred health care costs in IBD.

Despite the relatively long recall period of 1 year, we found a high concordance between self-reported and administrated number of hospitalizations, surgeries, diagnostic procedures, and the use of anti-TNF compounds. Our findings are in line with the only published study on this subject, which reported a comparable high sensitivity and specificity of 82% and 97% for self-reported IBD-related hospitalizations over the preceding year in a population-based IBD cohort performed in Canada.[9] Comparable results were published for self-reported hospitalizations over the past 6 months in patients with osteoarthritis (95% accuracy, r = 0.65)[5] and diabetes (kappa statistics 0.64–0.80).[4,8] For current medication used for a specific indication, a recall sensitivity of 88% was concluded from a public health survey.[14] To our knowledge, we are the first to establish self-report as a valid tool to study the incurred costs of IBD-related health care. For IBD, no studies have been performed in which the number of self-reported diagnostic procedures, surgeries, and the use of anti-TNF compounds were compared with those registered in an administrative database. The high response rate of 95% underscores the validity of our findings.

Using multivariable analysis, we identified current flares and having a pouch as independent factors for a poor recall. Patients with a poor recall both overreported and underreported their actual incurred costs of health care. In our data, patients currently suffering from a flare and patients with a pouch had a higher consumption of health care (data not shown), which may explain a diminished recall in these patients. Previous studies suggest that concordance with administrative data depends not only on the severity of disease but also on the level of cognition and age of respondents.[15] This could not be confirmed in our study. Of all patients, 69% correctly reported all consumed IBD- related health care over the past year. Obviously, the key cost drivers in IBD, identified in previous studies,[2,16] have a major impact on the personal life of patients and can therefore be expected to be easily remembered. To clarify differences between self-report and administrative data in the remaining 31% of patients, we examined these cases more closely. Reasons for over-reporting or underreporting health care utilization could be ascribed to the relative long recall period of a year, to multiple medical examinations and doctors' visits, or to the patient's unfamiliarity with medical terminology. Previous studies suggest that factors that affect accuracy include recall time frame, type of utilization, utilization frequency, questionnaire design, mode of data collection, and memory aids and probes.[15]

Our study design is subject to some potential flaws. Administrative data entered into the database may not cover all consumed health care over the past year, as patients may have visited other hospitals in this recall period. Our single-center study approach precluded

adjusting for health care expenses consumed in other hospitals. Moreover, data obtained from medical records might also contain administrative imperfections, such as misclassifications. [17] However, administrative health data have been appraised and established as a reliable source of health care utilization.[18] Furthermore, although we identified current flares and the presence of a pouch as independent predictors for a diminished recall, our study was not powered to perform post hoc analysis of these differences. Initially, we performed a sample size calculation for design accuracy by means of a pilot study of the first 20 participants. With an intraclass correlation of r = 0.99 between the total costs of self-report and administrative data, we calculated a required sample size of n = 9 to reach a power of 96%. Finally, we chose to aim for a total inclusion around 100 patients to increase the accuracy of our further measurements. The included patient population may however not be large enough to detect predictors for a poor recall. Nonetheless, our results are consistent with the present literature and indicate an association of disease severity with a diminished recall.[15] Finally, we chose to include only the largest cost drivers in the questionnaire, responsible for 86.2% of total health care costs in CD and 60.6% in UC.[2] Data on the number of outpatient clinic visits, visits to the general practitioner, laboratory tests or diagnostic procedures other than computed tomography scans, magnetic resonance scans, or colonoscopies were not collected. Previous studies have shown that recall of doctors' visits is worse than that of hospitalizations.[5,9] The addition of these units in our analysis could have led to a weaker correlation between self-report and administrative data. However, as these items have been shown to have minor impact on total resource costs in IBD, we believe that our strategy reliably reflects the actual incurred health care costs in these patients.

In this study, we report a high concordance between the costs of self-reported health care utilization and administrative data over the past year in IBD. Using a recall period of 1 year, self-reported health care utilization reliably measures the majority of consumed health care in IBD.

ACKNOWLEDGMENTS

The authors thank the IBD Parelsnoer Institute for access to their information on study participants.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Patient questionnaire on self-reported healthcare utilization over the past year

Date | |_|_|_|_|_|_| Study no. | |_|_|_|_|_|_|

Were any of these medical tests performed in the preceding year?

Medical test **Number of tests in the preceding year**

□ Abdominal CT-scan | |_|_|

A CT-scan is an imaging test, using x-rays. A CT-scan of the abdomen visualizes the internal organs, tissues and vessels, and provides better detail than traditional x-rays.

□ Abdominal MRI-scan | |_|_|

An MRI-scan of the abdomen is an imaging test using a strong magnetic field to investigate the anatomy and physiology of the abdominal organs. It does not use radiation (x-rays).

□ Colonoscopy | |_|_|

A colonoscopy is a medical procedure that uses a small camera mounted on a long, flexible tube that can be passed through the anus. This technique enables a visual diagnosis of abnormalities or diseases of the large bowel or the distal part of the small bowel and grants the opportunity for biopsy or removal of polys or other lesions.

□ None of these tests

Did you use any of these medications in the preceding year?

□ Infliximab (Remicade®)

[if ticked] Start date | |_|_|_|_|_|_| dd/mm/jj

Stop date | |_|_|_|_| | or □ I'm still using

Infliximab Number of infusions received? | |_|_|

□Adalimumab (Humira®)

[if ticked] Start date | |_|_|_|_|_|_| dd/mm/jj

Stop date | |_|_|_|_|_| or □ I'm still using

Adalimumab What is de dose at a time? | |_|_| mg

What is the number of doses per 2 weeks?| |

None of these medication

Have you been admitted to the hospital in the preceding year because of your inflammatory bowel disease?

□ No

□ Yes, | |_| times

If ticked "yes":

□ First hospital admission:

On what date were you admitted to the hospital, and on what date were you discharged?

Date of admission | |_|_|_|_|_|_| Date of discharge | |_|_|_|_|_|_|

Were you admitted to the intensive care unit?

□ Yes, I spent | |_|_| days in the intensive care unit

□ No

□ Second hospital admission:

On what date were you admitted to the hospital, and on what date were you discharged?

Date of admission | |_|_|_|_|_| | Date of discharge | |_|_|_|_|_| |

Were you admitted to the intensive care unit?

□ Yes, I spent | |_|_| days in the intensive care unit

□ No

□ **Third hospital admission:**

On what date were you admitted to the hospital, and on what date were you discharged?

Date of admission | |_|_|_|_| | Date of discharge | |_|_|_|_| |

Were you admitted to the intensive care unit?

□ Yes, I spent | |_|_| days in the intensive care unit

No

Did you have surgery in the preceding year because of your inflammatory bowel disease?

□ Yes, resection of the distal part of the small bowel and the proximal colon

□ Yes, a resection of the distal past of the small intestine for the second time

□ Yes, a resection of a part of the large bowel

□ Yes, resection of the complete large bowel

□ Yes, surgery for a fistula or abscess

□ Yes, other, namely| |_|_|_|_|_|

□ No, I didn't receive surgery

Supplementary Table 2. Unit costs of resource use, expressed in 2014 Euros

	Cost price (€)	References
Hospitalisation	Cost price per day	
Medical ward		
University medical centre	615.60	1
Intensive care unit	2,337.12	1
Medication use	Costs price per 3 months	
Infliximab	5,144.18[a]	2
Adalimumab	4,625.84[b]	2
Surgery	Cost price per type of surgery[c]	
Ileocecal resection/ resection neoterminal ileum	1,255.04	3
Partial colectomy	1,829.56	3
Subtotal colectomy	1,829.56	3
Abcess surgery	178.08	3
Complex fistula surgery	2,440.12	3
Rectum amputation	3,337.94	3
Ileostomy	787.58	3
Diagnostic procedures	Cost price per type of diagnostic procedure	
Colonoscopy	364.42	3
CT scan	162.14	3
MRI scan	199.24	3

[a] Price based on average weight of 75 kg and 1.8 infusions per 3 months4.

[b] Price based on 6,5 injections per 3 months (81% administered adalimumab 40 mgs per 2 weeks) or 13 injections per 3 months (19% of patients administered adalimumab 80 mgs per 2 weeks)4.

[c] Days admitted at the surgical or medical ward were not included in the cost price of surgery, but assessed separately 4.

References of Supplementary Table 2:

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Supplementary Table 3. Baseline predictors for a diminished recall in inflammatory bowel disease patients

	Perfect recall (n, %)	Diminished recall (n, %)	P- value	Unadj. Odds ratio (95% CI)	Adj. Odds ratio
Low education	37 (52.9)	22 (71.0)	0.09	2.2 (0.9 – 5.4)*	2.3 (0.8 – 6.1)
Currently employed	39 (55.7)	14 (45.2)	0.33	0.7 (0.3 – 1.5)	-
Abdominal surgery in the past	11 (15.7)	10 (32.3)	0.06	2.6 (0.9 – 6.9)*	1.8 (0.6 – 5.4)
Fistula	17 (24.3)	5 (16.1)	0.36	0.6 (0.2 – 1.8)	-
Pouch	1 (1.4)	4 (12.9)	0.01	10.2 (1.1 – 95.6)*	10.7 (1.1 – 107.6)**
Stoma	7 (10.0)	4 (12.9)	0.67	1.3 (0.4 – 4.9)	-
Female gender	38 (54.3)	15 (48.4)	0.58	0.8 (0.3 – 1.8)	-
Medication use	42 (61.4)	19 (61.3)	0.99	1.0 (0.4 – 2.4)	-
Current smoking	9 (12.9)	2 (6.5)	0.34	0.5 (0.1 – 2.3)	-
Age (per year)	52.1 (15.1)	52.9 (15.0)	0.79	1.0 (1.0 – 1.0)	-
Comorbidity	25 (35.7)	14 (45.2)	0.43	1.5 (0.6 – 3.5)	-
Current flare	14 (20.0)	12 (38.7)	< 0.05	2.5 (1.00 – 6.40)*	3.5 (1.3 – 9.6)**
Crohn's disease	46 (65.7)	24 (77.4)	0.24	1.8 (0.7 – 4.7)	-

**= p <0.2; **=p<0.05; CI: Confidence interval*

CHAPTER 2.2

The evolution of costs of inflammatory bowel disease over two year follow-up

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ABSTRACT

Background: With the increasing use of anti-TNF therapy in inflammatory bowel disease (IBD), a shift of costs has been observed with medication costs replacing hospitalization and surgery as major cost driver. We aimed to explore the evolution of IBD-related costs over two years of follow-up.

Methods and Findings: In total 1,307 Crohn's disease (CD) patients and 915 ulcerative colitis (UC) patients were prospectively followed for two years by three-monthly web-based questionnaires. Changes of healthcare costs, productivity costs and out-of-pocket costs over time were assessed using mixed model analysis. Multivariable logistic regression analysis was used to identify costs drivers. In total 737 CD patients and 566 UC were included. Total costs were stable over two years of follow-up, with annual total costs of €7,835 in CD and €3,600 in UC. However, within healthcare costs, the proportion of anti-TNF therapy-related costs increased from 64% to 72% in CD ($p<0.01$) and from 31% to 39% in UC ($p<0.01$). In contrast, the proportion of hospitalization costs decreased from 19% to 13% in CD ($p<0.01$), and 22% to 15% in UC ($p < 0.01$). Penetrating disease course predicted an increase of healthcare costs (adjusted odds ratio (adj. OR) 1.95 (95% CI 1.02–3.37) in CD and age <40 years in UC (adj. OR 4.72 (95% CI 1.61–13.86)).

Conclusions: IBD-related costs remained stable over two years. However, the proportion of anti-TNF- related healthcare costs increased, while hospitalization costs decreased. Factors associated with increased costs were penetrating disease course in CD and age <40 in UC.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), are characterized by chronic relapsing intestinal inflammation that may lead to severe complications and disability. Therefore, IBD represent a high economic burden to society.[1–8] The early onset and chronicity of IBD profoundly affects work productivity with accompanying economic losses mainly resulting from sick leave and work disability accounting for up to 50% of the total costs.[1,2,5–8]

With the introduction and increasing use of anti-TNF therapy in IBD, a major shift of costs has been observed with medication costs replacing in-patient care, such as hospitalization and surgery, as the greatest source of healthcare expenditure.[1] Most previous cost studies in IBD, however, relied on a single measurement of costs and were performed before the introduction of anti-TNF therapy in IBD.[2,3,7–10] Furthermore, only a limited number of studies have aimed to identify factors predicting IBD-related costs.[1,4,10,11]

The 'Costs Of Inflammatory bowel disease in the Netherlands' or COIN study has been initiated to generate longitudinal cost data in order to assess the impact of anti-TNF therapy on IBD-related costs. In the present study we aimed 1) to assess the evolution of costs of IBD over a period of two years, 2) to explore the contribution of healthcare, productivity and out-of- pocket costs on IBD-related costs; and 3) to identify predictors for high costs over two years of follow-up.

MATERIAL AND METHODS

Study design and patient population

From October 2010 to October 2011 we invited all IBD patients aged 18 years or older from seven university hospitals and seven district hospitals to participate in the COIN study by letter (Fig. 1).
A secure web-based questionnaire was developed to obtain baseline characteristics and collect cost data on a three-month basis during two years of follow-up. The cohort organisation and study follow-up protocol have been described in detail elsewhere.[1] The study was centrally approved by the Ethics Committee of the University Medical Centre Utrecht.

Data collection

Demographic characteristics included gender, age, age at diagnosis, education level, work status, family history, and smoking status. Clinical characteristics included subtype of IBD, disease duration and localization, disease behaviour, stoma or pouch surgery, and clinical dis- ease activity.
In accordance with Drummond et al.,[12] we distinguished three main IBD-related cost categories including healthcare costs, productivity losses and patient costs. Applying the human capital approach, productivity losses were estimated by multiplying the self-reported number of sick leave days from both paid and unpaid (i.e. voluntary work) work of patients and the caregivers taking care of the sick persons by age- and sex-specific productivity losses. A work- week was assumed to have at maximum of five working days. Patient costs were calculated according to patient specifications. Reference prices used in the COIN study are described in Supplementary Table 1. All costs are expressed in 2011 euros, using Dutch consumer price index when appropriate. No discounting was applied, given the limited follow-up period of two years. Potential predictive variables were identified from earlier studies on predictors for poor clinical outcome or high healthcare-or productivity losses (Supplementary Table 2).

Statistical analysis

Data analysis was performed using SPSS version 18.0. Descriptive statistics were used to characterize patients with CD and UC. We report means with a standard deviation (SD) and medians with an interquartile range (IQR). Comparisons between CD and UC patients were analysed with Student's t-test for continuous variables and $\chi 2$ for dichotomous variables. To compare medians, the Mann-Whitney U test was used. Costs were reported as mean cost/ patient with a 95% confidence interval.

To control equality between the study population (i.e. responders) and the patients who were lost to follow-up over time (i.e. non-responders) we performed a non-responder study. To account for missing data and repeated measurements, we used a generalized mixed model to compare costs between different subgroups.

We performed a multivariate logistic regression analysis to identify factors predicting increase of healthcare costs over two-years of follow-up. As a dependent variable we used the 10 percent of patients who displayed the highest increase in healthcare costs over two years of follow-up. Variables that reached borderline significance ($p<0.1$) in the univariate analysis were considered for inclusion into the multivariate models. We fitted separate models for UC and CD. P-values <0.05 were considered statistically significant.

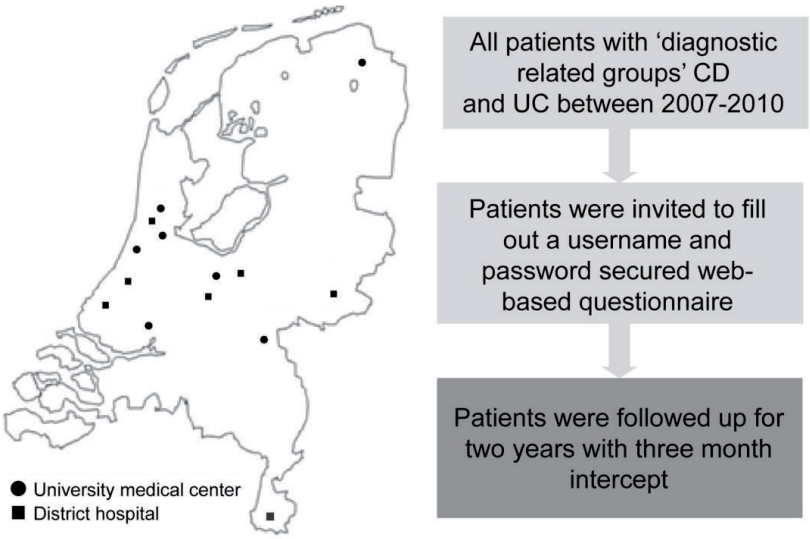

Fig.1: Design of the COIN study.

RESULTS

Study population

At baseline, 1,307 CD patients and 915 UC patients were included. The two-year follow-up questionnaire was filled-out by 736 CD patients and 566 UC patients (response rates of 47% and 54%, respectively). Additional response rates per time point are provided in Supplementary Table 3. From the patients who were lost to follow-up, 10 subjects died during the follow-up period, 54 were unreachable due to automatic email response bouncing our request (possibly due to a change of email address), 153 withdrew consent and 1,049 were lost for unknown reasons. Responders were older ($p<0.01$) and had longer disease duration ($p<0.01$) as compared to non-responders (Supplementary Table 4).

The baseline characteristics of the study population completing the two-year follow-up are described in Table 1. CD patients were more often females (60% versus 46%, $p<0.01$), smokers (19% versus 8%, $p<0.01$), and had a higher probability of previous abdominal surgery (56% versus 19%) compared to UC patients. CD patients were more frequently treated with immunomodulators (36% versus 23%, $p<0.01$) and/or anti-TNF (21% versus 4%, $p<0.01$) as compared to UC patients.

Table 1. Demographic and disease characteristics of the study population. SD: Standard deviation; IQR: Interquartile range; n/a: not applicable; NS: notsignificant.

	CD n = 737	UC n = 566	P-value
Male gender (%)	295 (4.0)	300 (53.0)	<0.01
Age—years (± SD)	50.5 (13.5)	52.4 (12.9)	0.01
Smoking (%)			<0.01
Current	137 (18.6)	45 (8.0)	
Never	382 (51.8)	336 (59.4)	
Ex-smoker	218 (29.6)	185 (32.7)	
Low education (%)	445 (60.4)	314 (55.5)	0.08
Disease duration—median (IQR)	18.2 (10.118.2)	16.0 (9.0–16.0)	<0.01
Disease localisation (%)			
Large bowel	204 (27.7)	566 (100)	n/a
Small bowel	152 (20.6)		
Both small and large bowel	361 (49.0)		
Unknown	20 (2.7)		
Penetrating disease course (%)	400 (54.3)		n/a
Clinical remission (%)	618 (83.9)	452 (79.9)	0.06
Abdominal surgery (%)	416 (56.4)	106 (18.7)	<0.01
Medication use (%)			
Mesalazine	175 (23.7)	373 (65.9)	<0.01
Azathioprine	189 (25.6)	91 (16.1)	<0.01
Mercaptopurine	51 (6.9)	36 (6.4)	NS
Methotrexate	25 (3.4)	1 (0.2)	NS
Prednisone	37 (4.9)	31 (5.5)	NS
Budesonide	44 (6.0)	19 (3.4)	NS
Infliximab	72 (9.8)	14 (2.5)	<0.01
Adalimumab	85 (11.5)	5 (0.9)	<0.01

IBD-related costs

Over the two-year follow-up period, IBD-related costs did not change (Fig. 2A and Fig. 2B). The mean annual IBD-related costs were €7,835 (95% CI €7,235- €9,563) for CD patients and €3,600 (95% CI €2,865- €4,669) for UC patients. Healthcare costs accounted for the major part of the IBD-related costs, 81% (€6,326 (95% CI €5,241- €7,102)) in CD and 65% (€2,340 (95% CI €1,540- €3,105)) in UC. In addition, productivity losses accounted for 17% (€1,335 (95% CI €860- €2,130)) of the total costs in CD patients and 31% (€1,120 (95% CI €571- €1,891)) in UC patients, whereas out-of-pocket costs accounted for 2% (€174 (95% CI €95- €220) in CD and 4% (€140 (95%CI €110-€195) in UC. Associated healthcare costs per 3 months are displayed in Supplementary Table 5A and Supplementary Table 5B .
In Fig. 3A and 3B, the breakdown of healthcare costs over time in the CD and UC cohorts is depicted. Although the absolute healthcare costs did not change significantly over the two years of follow-up, the proportion of anti-TNF therapy-related costs increased from 64% to 72% in CD ($p<0.01$), and from 31% to 39% in UC ($p<0.01$). This was mainly due to an increased use of anti-TNF over two years of follow up. This increase was accompanied by a reduction of the proportion of hospitalization costs, which decreased from 19% to 13% in CD ($p<0.01$), and from 22% to 15% in UC ($p<0.01$). The proportion of healthcare costs due to surgery, outpatient clinic, other mediation use and diagnostic procedures remained stable over time (Supplementary Table 5C and Supplementary Table 5D).

Predictors of healthcare costs

In Table 2 the results of the multivariate analysis on predictors of healthcare costs are shown. In CD, penetrating disease course was associated with an increase of healthcare costs (adjusted odds ratio (Adj. OR) 1.95 (95% CI 1.02–3.37)). Furthermore, anti-TNF therapy (Adj. OR 0.09 (95% CI 0.02–0.12)) and disease activity (0.47 (95% CI 0.24–0.93)) at three months of follow- up were found to be associated with a decrease of healthcare costs over two years of follow-up. This was mainly due to discontinuation of anti-TNF therapy in 20% of CD patients with disease activity. In case of UC, only age <40 years (n = 225, 39.8% of the UC population) was found to independently predict an increase of healthcare costs (adj. OR 4.72 (95% CI 1.61– 13.86)). The percentage UC patients <40 years receiving Anti-TNF therapy increased from 4.9% at baseline to 9.9% over two years of follow up.

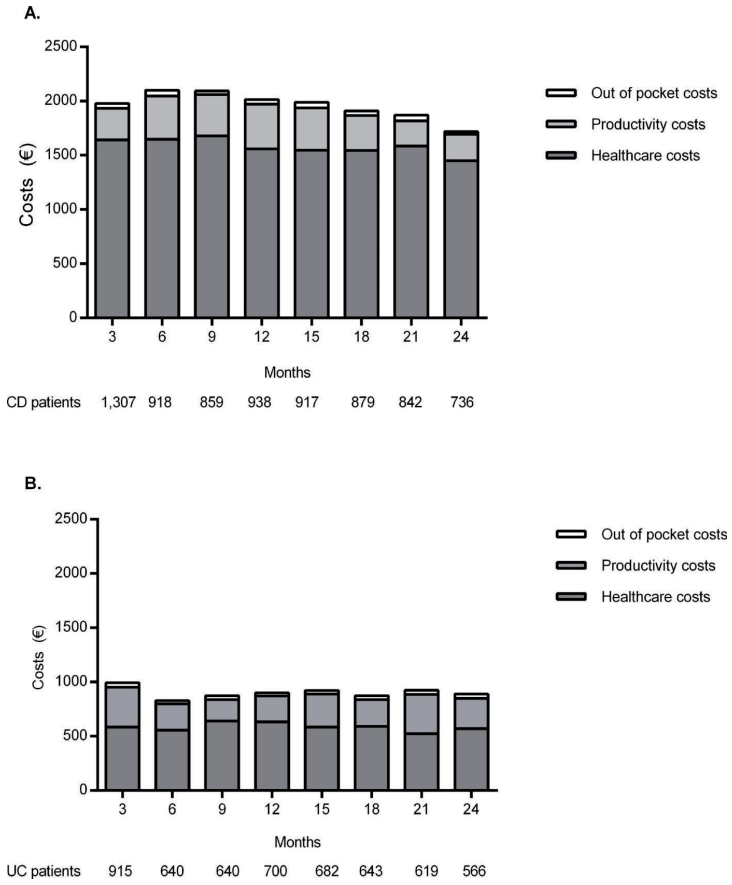

Fig. 2A: Three-monthly total costs per average CD-patient over two-year follow up. B. Three-monthly total costs per average UC-

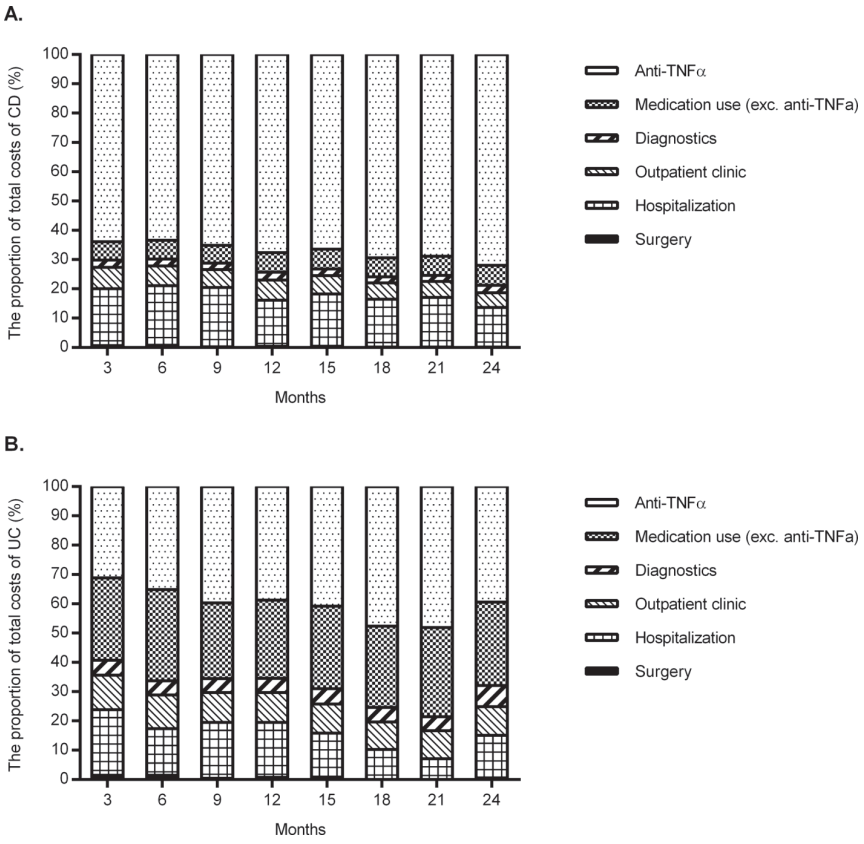

Fig. 3A: The proportion of healthcare costs for an average CD-patient over two-year follow up. B. The proportion of healthcare costs

Table 2. Multivariate logistic regression analyses of CD and UC patients with increase of healthcare costs as dependent

	CD		UC	
Variable	Adj. OR (95% CI)	p-value	Adj. OR (95% CI)	p-value
Age (at 3 months follow up)				
< 40 years	1.03 (0.54–1.98)	0.93	4.72 (1.61–13.86)	<0.01
>40 years (ref)	1		1	
Disease duration (at 3 months follow up)				
< 3 years	0.54 (0.17–1.68)	0.29	2.03 (0.55–7.54)	0.29
>3 years (ref)	1		1	
Abdominal surgery in the past				
Yes	0.68 (0.35–1.35)	0.27	3.36 (0.13–1.070)	0.07
No (ref)	1		1	
Anti-TNF therapy (at 3 months follow up)				
Yes	0.09 (0.02–0.12)	<0.01	0.14 (0.02–1.40)	0.10
No (ref)	1		1	
Disease activity (at 3 months follow up)				
Yes	0.47 (0.24–0.93)	0.03	-	
No (ref)	1			
Penetrating disease course				
Yes	1.95 (1.02–3.73)	0.04		
No (ref)	1			

DISCUSSION

The widespread use of anti-TNF in the treatment of patients with IBD has changed the healthcare landscape radically and has led to a major shift in cost profiles.[1] For the first time, we prospectively show in a large longitudinal study that IBD-related costs remain stable over a period of two years. In this period, we observed an ongoing shift of cost profiles with an increasing proportion of anti-TNF-related healthcare costs and a reduction of hospitalization costs.

Most of the IBD-related costs were incurred by anti-TNF therapy, both in CD and UC patients. The present data underscore our previous observations that healthcare expenditures in IBD shift from costs related to hospitalization and surgery to costs driven by medication use.[1] Due to the differences in study design and study populations, it is difficult to compare our results with other studies. For example, the recently published EPICOM cost data from a population-based inception cohort of patients in the first year after the diagnosis reported that the main cost drivers were investigative procedures (21%), surgical procedures (26%) and anti- TNF therapy (15%).[13] Interestingly, 20% and 4% of their CD and UC patients were already on anti-TNF therapy in the first year after diagnosis, which is almost identical to the rates observed in our cohort (21% in CD and 3% in UC).

An important observation is the ongoing rise of anti-TNF therapy-related costs, with a concurrent reduction of hospitalization costs. A similar trend in increase of anti-TNF therapy-related costs has been found in rheumatoid arthritis.[14,15] In two national registry cost-of-illness studies covering 20-years of follow-up, a downward trend for all costs, apart from the costs for anti-TNF, therapy has been reported. The decline of costs related to hospitalization in IBD is consistent with the observed decrease in surgery and hospitalisation rates in population- based studies.[16,17]

Even though healthcare cost differ to a large extend between Western countries, comparable trends in treatment paradigms should have induced the same alterations in cost profiles as observed in our study. For example, Kappelman et al. studied healthcare costs using medical and pharmacy claims from an administrative database between 2003 and 2004, in which 10% of all CD patients had at least two claims of infliximab infusions.[18] In this study, pharmaceutical claims accounted for the largest proportion of healthcare costs (35%), from which infliximab was the most costly medication.

The large sample size and longitudinal data enabled us to study predictors of healthcare costs over time. In CD, penetrating disease was found to be associated with an increase of costs over two years of follow-up. This can be attributed to the fact that a penetrating disease is a predictor of poor outcome in CD, resulting in frequent surgery and hospitalizations.[19–21] Furthermore, this complication of CD is often treated with anti-TNF compounds (26.9% in our cohort, data not shown).

In UC patients younger than 40 years of age, an increase of healthcare costs was encountered as well. We found a 100% increase of anti-TNF use among young UC patients during two

years of follow-up. This finding is in line with previous studies in which younger age in UC was found to be associated with a more severe disease course and an increased risk of relapses. [22–24] Furthermore, young age is associated with more extended colitis in which escalating therapy towards anti-TNF medication or surgery is frequently required. [25] In contrast, anti- TNF therapy and disease activity were associated with a decrease of healthcare costs. This was mainly due to the fact that in these patients, anti-TNF therapy was eventually discontinued. Whether this was due to treatment failure, side effects or cessation of this drug because of treatment success could not be discerned from our data.

Our study has several limitations. First, an inherent limitation of a longitudinal study using a web-based questionnaire design is the high rate of loss to follow-up. We tried to reduce the impact of this problem by using mixed models to correct for missing values. Furthermore, we performed a non-responder study, which showed that responders (i.e. the individuals completing all questionnaires) were older and had a longer disease duration. Since costs in elderly IBD patients are lower than in younger patients,[26] we may have underestimated total healthcare costs. Interestingly, even in this relatively old population, the prescription of anti-TNF therapy increased over a follow-up period of two years. Furthermore, we did not have clinical data such as endoscopic or laboratory markers of disease activity at our disposal. Potentially, these might prove to be important determinants of future healthcare costs as well. For example, deep ulcers or high faecal calprotectin levels may predict a severe disease course with associated high costs.

In conclusion, there is an apparent shift in cost profiles from surgery and hospitalization towards anti-TNF therapy. However, total IBD costs remain remarkably stable over time, suggesting that the anti-TNF-related costs are compensated by a reduction of hospitalization costs. This may corroborate the notion that investment in expensive medical therapy might be cost-effective from a pharmaco-economical point of view, presuming that a reduction in hospital admission is equal with an improvement in quality-of-life. Whether long-term anti-TNF therapy is truly cost-effective in IBD has yet to be determined. Further careful monitoring of changes in the costs of care for IBD patients will aid timely, sensible economic decision- making.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. unit costs of resource use for the year 2011

	Unit cost price (€)
	Unit cost price per visit
Outpatient clinic consultations	
District hospital	64.64
University medical centre	130.29
Emergency room	152.51
General practitioner	
Visit (day-time)	28.28
Home visit (day-time)	43.43
Visit (weekend/ night-time)	82.00[a]
Home visit (weekend/ night-time)	123.00[a]
	Unit cost price per hour
IBD or stoma nurse – per hour	44.50
Dietician – per hour	48.70
Hospitalisation	Unit cost price per day
Medical ward	
General hospital	439.35
University medical centre	580.75
Intensive care unit	2204.83
Medication use	Unit costs price per 3 months
Mesalazine	UC: 212.42[b] CD: 246,90[c]
Prednisone	15.09 [d]
Budesonide	189.81[e]
Azathioprine - 150 g/day	90.62[f]
Mercaptopurine - 50 mg/day	90.62[g]
Methotrexate - 15 mg/ week	248,44[h]
Infliximab	4,853[i]
Adalimumab	4,364[j]
Surgery	Unit cost price/ surgery [k]
Ileocecal resection/ resection neoterminal ileum	1,184.00
Partial colectomy	1,726.00
Subtotal colectomy	1,726.00
Abcess surgery	168.00
Complex fistula surgery	2,302.00
Rectum amputation	3,149.00
Ileostomy	743.00

Diagnostic procedures	Unit cost price/ diagnostic procedure	
Colonoscopy	343.79	
CT scan	152.96	
MRI scan	187.96	
Abdominal X-ray	43.38	
Ultrasonography	37.67	
DXA scan	84.47	
Laboratory	18.06l	
Sick leave from paid work (patient)	Productivity losses per working hour	
	Females	Males
15-19 years	8.94	9.84
20-24 years	17.52	18.11
25-29 years	24.09	24.67
30-34 years	28.09	30.24
35-39 years	29.84	34.71
40-44 years	29.64	37.40
45-49 years	29.49	39.09
50-54 years	29.84	39.84
55-59 years	30.09	40.17
60-64 years	29.24	39.91
Sick leave from unpaid work (patient and caregiver)	Productivity losses per working hour	
	12.96	

[a] Price based on average cost price of 55 general practitioners (weekend/evening/night).[b] Price based on average dose of 2000 mg/day during 91 days. [c] Price based on average dose of 2400 mg/day during 91 days. [d] Price based on average dose of 10 mg/day during 91 days.

[e] Price based on average dose of 6 g/day during 91 days.

[f] Price based on average dose of 150 mg/day during 91 days.

[g] Price based on average dose of 50 mg/day during 91 days.

[h] Price based on average dose of 15 mg/ week during 13 weeks.

[i] Price based on average weight of 75 kg and 1.8 infusions per 3 months.

[j] Price based on 6,5 injections per 3 months (81% administered adalimumab 40 mgs per 2 weeks) or 13 injections per 3 months (19% of patients administered adalimumab 80 mgs per 2 weeks).

[k] Days admitted at the surgical or medical were not included in the cost price of surgery, but assessed separately .

[l] Price based on full blood count and differential, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, y- glutamyl transferase, sodium, potassium, creatinine, albumin.

[m] For patients with an ileostomy costs for caring for the stoma were based on a standard care package. This is based on the assumption of an exchange of base disk 4 times per week and of the ileostomy bag twice/day.

Supplementary Table 2. Possible predictors for future high costs

Variable	Study references		
	Predictors of healthcare costs	Predictors of productivity losses or costs	Predictors of poor prognosis
Female gender	(1)	(4)	(6;7)
Age	(2;3)	(2;4;5)	(6-10)
Smoking			(7)
Education level		(4)	
Short disease duration	(1)		
Penetrating disease course	(2;11)		(8;10;12)
Disease localisation			(6;9;10;12)
Disease activity/ flare	(1;2;11)	(2;4;5;11)	(7;13)
Hospitalization	(1)		
Surgery		(4;5)	
Ileostomy	(11)	(4)	
Anti TNFa therapy	(1)		
Steroids		(4;5)	(8;12)
Joint complaints		(4)	
Chronic back pain		(4)	
Depression		(4)	

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Supplementary Table 3. Number of responders per time point

Time point	Number of CD patients	Number of UC patients
Baseline	1,558	1,056
3 months	1,307	915
6 months	918	640
9 months	859	640
12 months	938	700
15 months	917	682
18 months	879	643
21 months	842	619
24 months	736*	566*

Response rate CD: 47%, UC 54%

Supplementary Table 4. Comparison between patients who completed the two year follow up (responders) and patients who were lost to follow up (non responders)

	CD		UC	
	Responders n=737	**Non-responders n=821**	**Responders n= 566**	**Non-responders n=490**
Male gender (%)	295 (40.0)	279 (34.0)	300 (53.0)	228 (46.5)
Age – years (± SD)	50.5 (13.5)	45.6 (13.8)	52.4 (12.9)	48.0 (13.7)
Disease duration – median (IQR)	18.2 (10.1-18.2)	16.8 (11.4)	16.0 (9.0-16.0)	13.9 (10.0)
Disease localisation (%)				
Large bowel	204 (27.7)	227 (27.6)	566 (100)	490 (100)
Small bowel	152 (20.6)	154 (18.8)	n/a	n/a
Both small and large bowel	361 (49.0)	407 (49.6)	n/a	n/a
Unknown	20 (2.7)	33 (4.0)	n/a	n/a
Penetrating disease course (%)	348 (47.2)	396 (48.2)	n/a	n/a
Disease activity (%)	618 (16.1)	117 (14.3)	452 (20.1)	98 (20.0)
Abdominal surgery (%)	416 (56.4)	427 (52.0)	106 (21.3)	89 (18.2)

SD: Standard deviation; IQR: interquartile range; n/a: not applicable

Supplementary Table 5A. Average healthcare costs/patient per 3 months in CD patients (€)

Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti- TNFa)	Anti- TNFa
3	996	319.23	119.93	40.81	103.84	1,048.1
6	13.33	334.31	111.47	38.14	106.12	1,042.55
9	3.34	340.89	102.75	35.9	103.09	1,093.27
12	7.63	244	107.52	41.36	103.97	1,053.93
15	7.41	275.51	96.78	35.06	103.62	1,027.32
18	1.53	251.89	86.66	32.65	100.53	1,070.62
21	2.24	268.91	85.61	33.66	102.28	1,090.59
24	1.83	195.61	74.1	36.34	99.24	1,044.54

Supplementary Table 5B. Average healthcare costs/patients per 3 months in UC patients (€)

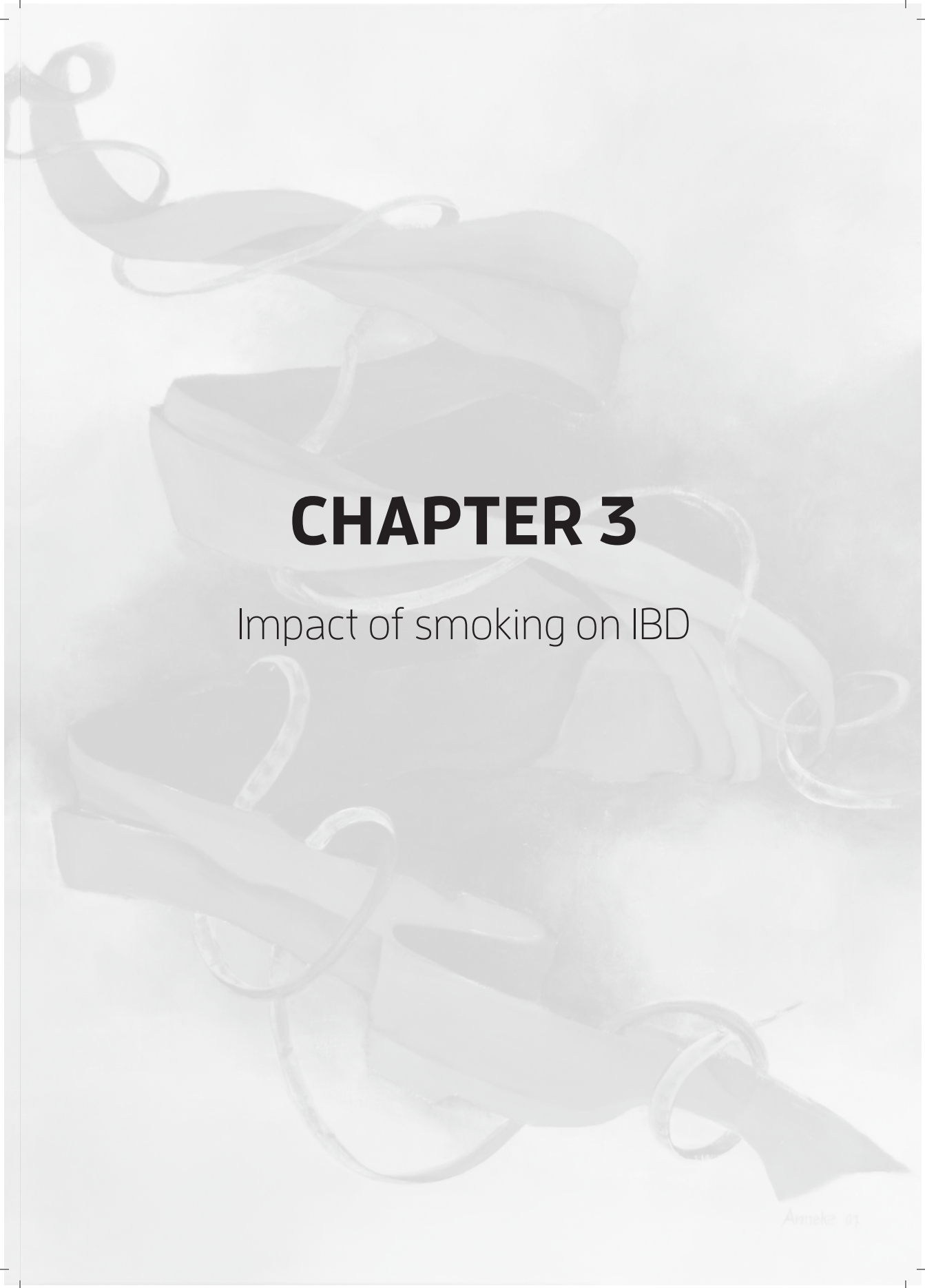
Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti- TNFa)	Anti- TNFa
3	8,36	130,58	68,46	29,95	163,87	181.35
6	8,09	87,89	63,67	26,81	172,27	194.09
9	2,7	122,25	64,56	30,7	164,98	253.22
12	5,17	118,17	63,97	30,37	169,29	243.99
15	5,06	87,24	58,05	30,68	163,78	237.63
18	0	60,47	55,21	29,33	163,73	280.71
21	0	37,19	50,37	24,51	159,47	251.6
24	3,05	82,87	55,23	40,84	161,56	223.72

Supplementary Table 5C. Proportion of healthcare costs in CD (%)

Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti- TNFa)	Anti- TNFa
3	0.61	19.44	7.30	2.49	6.32	63.84
6	0.81	20.31	6.77	2.32	6.45	63.34
9	0.20	20.30	6.12	2.14	6.14	65.11
12	0.49	15.66	6.90	2.65	6.67	67.63
15	0.48	17.82	6.26	2.27	6.70	66.46
18	0.10	16.32	5.61	2.11	6.51	69.35
21	0.14	16.98	5.41	2.13	6.46	68.88
24	0.13	13.47	5.10	2.50	6.84	71.95

Supplementary Table 5D. Proportion of healthcare costs in UC (%)

Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti- TNFa)	Anti- TNFa
3	1.44	22.41	11.75	5.14	28.13	31.13
6	1.46	15.90	11.52	4.85	31.16	35.11
9	0.42	19.15	10.11	4.81	25.84	39.66
12	0.82	18.73	10.14	4.81	26.83	38.67
15	0.87	14.98	9.97	5.27	28.12	40.80
18	0.00	10.26	9.37	4.98	27.78	47.62
21	0.00	7.11	9.63	4.69	30.48	48.09
24	0.54	14.61	9.74	7.20	28.48	39.44



CHAPTER 3

Impact of smoking on IBD

CHAPTER 3.I

Smoking is associated with extra-intestinal manifestations in inflammatory bowel disease

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ABSTRACT

Background and aims: Smoking affects the course of disease in patients with ulcerative colitis (UC) and Crohn's disease (CD). We aimed to study the association between smoking and extra-intestinal manifestations (EIMs) in inflammatory bowel disease (IBD).

Methods: We cross-sectionally explored the association between smoking and EIMs in IBD in three cohort studies: (1) the COIN study, designed to estimate healthcare expenditures in IBD; (2) the Groningen study, focused on cigarette smoke exposure and disease behaviour in IBD; and (3) the JOINT study, evaluating joint and back manifestations in IBD.

Results: In the COIN, Groningen and JOINT cohorts, 3030, 797 and 225 patients were enrolled, of whom 16, 24 and 23.5% were current smokers, respectively. Chronic skin disorders and joint manifestations were more prevalent in smoking IBD patients than in non-smokers (COIN, 39.1 vs 29.8%, p <0.01; Groningen, 41.7 vs 30.0%, p <0.01) in both CD and UC. In the JOINT cohort, smoking was more prevalent in IBD patients with joint manifestations than in those without (30.3 vs 13.0%, p <0.01). EIMs appeared to be more prevalent in high- than in low-exposure smokers (56.0 vs 37.1%, p = 0.10). After smoking cessation, the prevalence of EIMs in IBD patients rapidly decreased towards levels found in never smokers (lag time: COIN cohort, 1–2 years; Groningen cohort, within 1 year).

Conclusions: There is a robust dose-dependent association between active smoking and EIMs in both CD and UC patients. Smoking cessation was found to result in a rapid reduction of EIM prevalence to levels encountered in never smokers.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic intestinal disorder comprising Crohn's disease (CD) and ulcerative colitis (UC). In Europe the incidence rates are currently estimated to be 5.4 per 100000 person-years for CD and 8.2 per 100000 person-years for UC.[1]

IBD is frequently associated with extra-intestinal manifestations (EIMs). The most common EIMs involve the joints, the skin and the eyes.[2] The prevalence of EIMs in IBD patients ranges from 6 to 38%, and patients with CD are more prone to the development of EIMs than UC patients.[3-8]

The influence of smoking on disease activity in patients with IBD is now well established. Remarkably, smoking affects the course of disease differently in CD and UC, having a negative effect on the course of CD and a beneficial effect in UC.[8-10] The association between smoking and EIMs in IBD is currently largely undefined. As the burden of EIMs for these patients is high and its treatment remains a challenge, a better understanding of risk factors for EIMs in IBD is warranted. An increased prevalence of EIMs in smoking IBD patients was reported in two recent studies.[11,12] These studies did not correct for disease activity and were not conclusive with respect to the potential difference between CD and UC. Importantly, no studies have been performed that are solely focused on the association between smoking and EIMs in IBD.

We hypothesized that EIMs are more prevalent in smoking CD patients, as smoking may induce an inflammatory response both inside and outside the gut. Because smoking is associated with a more benign disease course in UC, EIMs might be less prevalent in smoking UC patients.

The primary aim of the current cohort study was to examine the putative association between smoking and EIMs in IBD. Our secondary aims were to detect a possible dose–response relationship between smoking and EIMs and to test whether smoking was associated with specific phenotypes of joint manifestations in IBD.

METHODS

Study design and study population

We explored the association between smoking and EIMs in three IBD cohorts.
The COIN (Costs of Inflammatory Bowel Disease in the Netherlands) study[13] is a large multicentre cohort study initiated in 2010 to prospectively assess the quality of life and the direct and indirect IBD-related healthcare and non-healthcare costs. All patients from seven university medical centres and seven general hospitals aged 18 years or older were eligible for participation. This study is still ongoing.
The Groningen study was a prospective single-centre cohort study, mainly designed to evaluate the clinical effects of smoking on IBD.[10] The cohort population consisted of consecutive IBD patients who visited the outpatient department of the University Medical Centre Groningen between January 1995 and October 2005. Patients with a concomitant liver transplantation were excluded.
The JOINT study[14] was a single-centre prospective cohort study focused on IBD patients with and without back pain and/or peripheral joint complaints. The study population consisted of consecutive IBD patients who were systematically assessed by a multidisciplinary team of gastroenterologists and rheumatologists at the Leiden University Medical Centre between July 2009 and February 2010. All included patients were followed for 12 months.
All three studies were approved by local medical ethics commit-tees. More details on study designs can be found in the corresponding references.[10,13,14]

Data collection

For the COIN cohort, participants were invited to fill out a baseline questionnaire followed by 3-monthly questionnaires. To control equality between the cohort population and the patients who did not respond, demographics and disease characteristics were compared between responders and non-responders.[13] For the current study, demographic data, smoking status (both current and previous, including date of smoking cessation, if applicable), EIMs and disease severity (self-reported flares) were extracted at baseline and medication use was extracted after 3 months of follow-up.
In the Groningen cohort, patients received a detailed questionnaire about their smoking behaviour. For the patients who returned the questionnaire, clinical characteristics and outcome variables were assessed by both a retrospective analysis of medical records and the collection of outcome variables during follow-up. For the current study, we focused on information on smoking behaviour (both current and previous, including number of pack-years[15] and date of smoking cessation, if applicable) and EIMs from medical records.
In the JOINT cohort, data on medical history (EIMs, family his-tory and medication use), physical examination (palpation of the joints, entheses and digits), laboratory tests

(C-reactive protein and HLA-B27) and radiological examinations of affected joints were collected from all enrolled patients. Based on these assessments, patients were categorized into two study arms: (1) patients with joint and/or back pain for ≥3 months and/or peripheral joint pain or swelling during the last year; and (2) patients without joint and/or back pain. Peripheral arthritis was defined as the presence of both pain and swelling in one or more joints and arthralgia was defined as non-inflammatory joint pain. At baseline, demographic characteristics (including current smoking status) were collected.

Definition of extra-intestinal manifestations

In the COIN cohort, EIMs were defined as the presence of self-reported joint complaints (arthritis and chronic back pain) and/or chronic skin disorders. In the Groningen cohort, EIMs were defined as joint complaints (arthralgia, enthesitis, arthritis, sacro-iliitis and ankylosing spondylitis) and/or skin disorders (erythema nodosum, pyoderma gangrenosum, psoriasis and hidradenitis suppurativa), as extracted from medical records, confirmed by medical specialists. The JOINT study was focused on joint manifestations, which were objectified by an extensive assessment by medical specialists.

Data analysis

The association between smoking and EIMs was cross-sectionally analysed in all three cohorts separately. We compared the prevalence of EIMs between smokers, non-smokers and ex-smokers using the $\chi 2$ test or Fisher's exact test, as appropriate. In the COIN and Groningen cohorts, we performed univariable and multivariable logistic regression analyses to test whether current smoking and ex-smoking were independent predictors of EIMs. Multivariable analysis was per-formed with co-variables with a p value <0.20 in the univariable analysis. Furthermore, we investigated the putative dose–response relationship between smoking and EIMs in the Groningen cohort. First, we compared the prevalence of EIMs between high (>10 pack-years) and low (≤10 pack-years) exposure smokers using the $\chi 2$ test. Second, we compared the prevalence of EIMs between inclining levels of smoke exposure, measured by pack-years,[15,16] using one-way ANOVA with the Tukey and/or Games–Howell post hoc multiple comparison test for trends. Participants in the JOINT cohort were categorized based on the presence or absence of peripheral joint manifestations or back pain. Therefore, we compared the prevalence of smoking between patients with and without joint manifestations in this cohort using the $\chi 2$ test. Moreover, we explored the association between smoking and specific phenotypes of joint manifestations by comparing the distribution of phenotypes between smokers and non-smokers using the $\chi 2$ test. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21 (Armonk, NY).

Table 1. Baseline characteristics.

	COIN cohort	Groningen cohort	JOINT cohort
Number of patients	3030	797	255
Demographics			
Male gender, n (%)	1325 (43.7)	326 (40.9)	97 (38.0)
Type of IBD, n (%)			
Crohn's disease	1558 (51.4)	428 (53.7)	186 (72.9)
Ulcerative colitis	1054 (34.8)	307 (38.5)	69 (27.1)
Unspecified	418 (13.8)	62 (7.8)	0 (0.0)
Age, years, mean (SD)	51.6 (13.7)	41.0 (14.5)	43.1 (13.5)
Low education level, n (%)	1898 (62.6)	468 (58.7)	135 (52.9)
Currently employed, n (%)	1557 (51.4)	470 (59.0)	157 (61.6)
Smoking status, n (%), IBD, CD, UC			
Current	486 (16.0), 329 (21.1), 95 (9.0)	188 (24.0), 139 (33.2), 38 (12.6)	60 (23.5), 51 (27.4), 9 (13.0)
Never	1605 (53.0), 781 (50.1), 603 (57.1)	304 (38.9), 133 (31.7), 142 (47.0)	98 (38.4), 61 (32.8), 37 (53.6)
Ex	939 (31.0), 448 (28.8), 358 (33.9)	290 (37.1), 147 (35.1), 122 (40.4)	97 (38.0), 74 (39.8), 23 (33.3)
Disease characteristics, Montreal classification, n (%)			
Location, n (%)			
L1, ileal	–	99 (33.9)	46 (24.7)
L2, colonic	–	62 (21.2)	40 (21.5)
L3, ileocolonic	–	105 (36.0)	83 (44.6)
L4, upper	–	4 (1.4)	2 (1.1)
L1–3 + L4	–	22 (7.5)	15 (8.1)
Behaviour of CD			
B1, non-stricturing/penetrating	–	130 (42.2)	109 (58.6)
B2, stricturing	–	46 (14.9)	38 (20.4)
B3, penetrating + perianal disease	–	132 (42.9)	39 (21.0), 55 (30.0)
Extension of UC, n (%)			
E1, ulcerative proctitis	–	33 (15.7)	7 (10.1)
E2, left-sided UC	–	63 (30.0)	23 (33.3)
E3, extensive UC (pancolitis)	–	114 (54.3)	39 (56.5)
UC severity, n (%)			
S1, clinical remission	–	22 (7.2)	–
S2, mild	–	64 (20.8)	–
S3, moderate	–	64 (20.8)	–
S4, severe	–	61 (19.8)	–
Unknown	–	96 (31.3)	–
Disease location, n (%)			
Small bowel	306 (19.6)	–	–
Large bowel	431 (27.7)	–	–
Small and large bowel	768 (49.3)	–	–
Penetrating disease in CD, n (%)	814 (52.2)		
Disease in remission, n (%)	2549 (84.2)	–	152 (59.6)
Stoma, n (%)	300 (9.9)	102 (12.8)	20 (7.8)
Pouch n (%)	167 (5.5)	9 (1.1)	13 (5.1)
Abdominal surgery in the past, n (%)	1143 (37.7)	250 (45.2)	107 (42.0)
Medication use, n (%), CD, UC*			
5-ASA	307 (23.5), 596 (65.2)	27 (6.3), 144 (46.9)	18 (9.7), 33 (47.8)
Steroids	134 (10.2), 70 (7.6)	63 (14.7), 30 (9.8)	9 (4.8), 5 (7.2)
Immunosuppressive drugs, (Aza + 6MP +MTX)	463 (35.4), 203 (22.2)	155 (36.2), 65 (21.1)	43 (23.1), 12 (17.4)
Anti-TNF	299 (22.9), 35 (3.8)	114 (26.6), 11 (3.6)	66 (35.5), 6 (8.7)
None	337 (25.8), 198 (21.7)	57 (13.3), 44 (14.3)	50 (26.9), 13 (18.8)

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; ASA, aminosalicylic acid; Aza, azathioprine; 6MP, 6-mercaptopurine; MTX, methotrexate; TNF, tumour necrosis factor.

*At 3 months of follow-up.

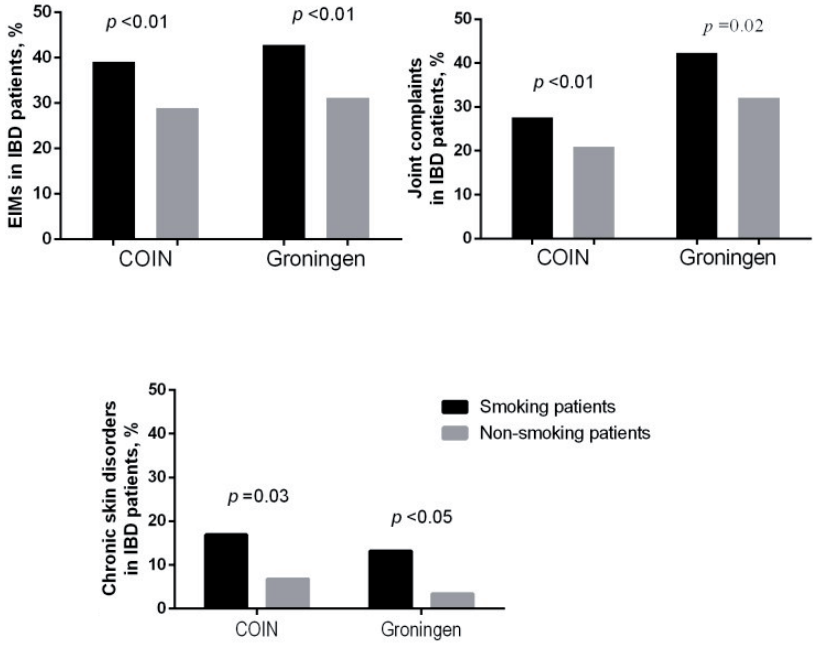

Fig.1: Prevalence of EIMs in smoking versus non-smoking IBD patients

Table 2. Association between smoking and extra-intestinal manifestations in inflammatory bowel disease.

	Study	Smoking patients (1)	Never-smoking patients (2)	Ex-smoking patients (3)	p-value, smoking vs non-smoking	p-value, (1 vs 2)	p- value, (1 vs 3)
Inflammatory bowel disease							
Total EIMs	COIN	190 (39.1)	432 (26.9)	325 (34.6)	<0.01	<0.01	0.10
	Groningen	75 (41.7)	87 (29.3)	86 (30.5)	<0.01	<0.01	0.01
Joint complaints	COIN	134 (27.6)	290 (18.1)	241 (25.7)	<0.01	<0.01	0.44
	Groningen	69 (42.3)	84 (31.6)	84 (32.4)	0.02	0.02	0.04
Chronic skin disorders	COIN	82 (16.9)	207 (12.9)	128 (13.6)	0.03	0.03	0.10
	Groningen	12 (6.8)	8 (2.7)	11 (4.0)	<0.05	0.04	0.19
Crohn's disease							
Total EIMs	COIN	140 (42.6)	235 (30.1)	167 (37.3)	<0.01	<0.01	0.14
	Groningen	64 (47.1)	51 (38.6)	58 (39.5)	0.12	0.16	0.20
Joint complaints	COIN	101 (30.7)	155 (19.8)	117 (26.1)	<0.01	<0.01	0.16
	Groningen	58 (46.4)	49 (39.5)	58 (41.4)	0.26	0.27	0.42
Chronic skin disorders	COIN	60 (18.2)	117 (15.0)	76 (17.0)	0.27	0.18	0.65
	Groningen	12 (9.0)	6 (4.6)	8 (5.6)	0.13	0.15	0.27
Ulcerative colitis							
Total EIMs	COIN	32 (33.7)	136 (22.6)	115 (32.1)	0.11	0.02	0.77
	Groningen	9 (25.7)	27 (19.6)	26 (22.8)	0.56	0.42	0.72
Joint complaints	COIN	24 (25.3)	92 (15.3)	86 (24.0)	0.11	0.02	0.80
	Groningen	9 (31.0)	26 (21.7)	24 (24.0)	0.34	0.29	0.45
Chronic skin disorders	COIN	12 (12.6)	63 (10.3)	38 (10.6)	0.50	0.49	0.58
	Groningen	0 (0.0)	2 (1.5)	3 (2.7)	0.39	1.00	1.00

IBD, inflammatory bowel disease; EIMs, extra-intestinal manifestations.

RESULTS

Study population

In the COIN cohort 3030 patients were enrolled; 16% of the patients currently smoked (CD 21.1%, UC 9.0%). There were no statistically significant differences between responders and non-responders.[13] In the Groningen cohort 797 IBD patients returned the questionnaire (97.2% response rate), of whom 24.0% were cur-rent smokers (CD 33.2%, UC 12.6%). In the JOINT cohort 255 patients (155 IBD patients with joint complaints, 100 without joint complaints) were enrolled. In this cohort 23.5% were current smokers (CD 27.4%, UC 13.0%). In the COIN cohort, ex-smoking CD and UC patients quit smoking a median of 10 years (interquartile range [IQR] 5–18) and 14 years (IQR 8–25) before inclusion. In the Groningen cohort, ex-smoking CD and UC patients quit smoking a median of 7 (IQR 2–14) and 13 (IQR 3–23) years before inclusion. In the JOINT cohort, ex-smoking CD and UC patients quit smoking a median of 10 years (IQR 3–19) and 14 years (IQR 5–27) before inclusion. Available baseline characteristics of all study participants are listed in Table 1.

Association between smoking and EIMs in IBD

The overall prevalence of EIMs in IBD was 31.3% in the COIN cohort and 32.3% in the Groningen cohort. EIMs were significantly more prevalent in the smoking IBD population than in non-smoking patients (COIN cohort, 39.1 vs 29.8%, $p < 0.01$; Groningen cohort, 41.7 vs 30.0%, $p < 0.01$) (Fig. 1). EIMs were more prevalent in current smokers than in never smokers (COIN and Groningen cohort, $p < 0.01$), and in the Groningen cohort also compared with ex-smokers ($p < 0.01$) (Table 2). In the COIN cohort smoking was associated with EIMs in both CD and UC patients, although more predominantly so in CD. Joint manifestations appeared to be more strongly associated with smoking than skin disorders.

Prevalence of smoking in IBD patients with joint complaints

In the JOINT cohort, smoking was more prevalent in IBD patients with joint manifestations than in patients without joint manifestations (30.3 vs 13%, $p < 0.01$). This association was found in both CD and UC patients (CD, 33.9 vs 15.4%, $p < 0.01$; UC, 17.6 vs 8.6%, $p = 0.03$). Joint manifestations in smokers were diagnosed after a mean of 17 years of tobacco exposure (standard deviation 13 years). Smoking was not associated with a specific localization of joint manifestations (axial pain, 8.5% in smokers vs 8.3% in non-smokers, $p = 0.53$; peripheral joint manifestations, 44.7% in smokers vs 54.6% in non-smokers, $p = 0.49$). However, smoking IBD patients more often experienced a combination of both axial and peripheral joint manifestations (46.9 vs 37.0%, $p = 0.01$). Smoking was not primarily associated with peripheral arthritis, as the prevalence was not significantly higher in smoking IBD patients

(p = 0.34). Arthralgia was found to be more prevalent in smoking IBD patients (48.3 vs 32.3% p = 0.02), especially in CD.

Multivariable analysis for the presence of EIMs in IBD

Adjusted for demographic data and disease severity, active smoking was associated with the presence of EIMs with an odds ratio (OR) of 1.52 in CD patients (95% confidence interval [CI] 1.15–2.01) and 1.75 in UC patients (1.07–2.84) of the COIN cohort (Supplementary Table 1). Female gender and higher age were also independently associated with the presence of EIMs in both CD and UC. The previous use of biologicals and a low level of education were found to be independent risk factors for EIMs in CD, and ex-smoking was an independent factor for EIMs in UC (OR 1.41, 95% CI 1.03–1.92). In the Groningen cohort, smoking was not an independent factor for EIMs in CD and UC (Supplementary Table 2). In this cohort, a low education level was found to be independently associated with EIMs in UC (adjusted OR 2.31, 95% CI 1.14– 4.70)

Dose–response relationship between smoking and EIMs in IBD

In the Groningen cohort, complete information on the quantity of total tobacco exposure was available for analysis in 95 currently smoking IBD patients (70 CD, 22 UC and 3 IBD unclassified). Although not statistically significant, EIMs appeared to be more prevalent in high-exposure smokers (>10 pack-years) than in low-exposure smokers (≤10 pack-years), which applied to CD but not to UC patients (IBD, 56.0 vs 37.1%, p = 0.10; CD, 64.7 vs 39.2%, p = 0.07; UC, 20.0 vs 33.3%, p = 0.57). Based on a subdivision of smoking patients into light smokers (0.1–20.0 pack-years), moderate smokers (20.1–40.0 pack-years) and heavy smokers (>40 pack-years), the prevalence of EIMs appeared to increase with higher levels of smoke exposure (IBD, 37.8, 50.0 and 60.0%, respectively; CD, 41.7, 50.0 and 100.0%). Meaningful statistical analysis in UC could not be performed due to the low number of cases. For the total IBD population, no statistical significant trend was found, but for CD a statistical significant difference in prevalence of EIMs between light smokers and heavy smokers was found ($p < 0.05$).

EIMs in ex-smoking IBD patients

The prevalence of EIMs in ex-smoking IBD patients and in patients who never smoked was comparable to that in the Groningen cohort (30.5 vs 29.3%, p = 0.95), which applied to both CD and UC. In the COIN cohort, the prevalence of EIMs was higher in ex-smoking patients than in never smokers (34.6 vs 26.9%, $p < 0.01$), which also applied to both CD and UC. However, when comparing the prevalence of EIMs between patients who recently quitted smoking and patients who quitted longer ago, we observed a rapid decline in prevalence

towards levels encountered in never smokers in both cohorts. In the Groningen cohort, IBD patients who quitted smoking >3 months ago appeared to have EIMs less often than patients who stopped smoking <3 months before inclusion (33.0 [n = 60] vs 57.1% [n = 7], p = 0.07). In the COIN cohort, the prevalence of EIMs in the ex-smoking IBD population appeared to decline if smoking was stopped for >1 year, since the prevalence of EIMs was 42.9% (n = 3) in patients who quit-ted smoking <1 year before inclusion compared with 30.9% (n = 17) in patients who quitted between 1 and 2 years before inclusion, although the difference was not statistically significant (p = 0.52).

DISCUSSION

This study, encompassing results from three different cohorts, has demonstrated a strong association between smoking and EIMs in IBD, and indicates a dose–response relationship, as EIMs appear to be more prevalent in heavy-smoking patients. Interestingly, the prevalence rates of EIMs rapidly declined to levels encountered in never-smoking patients when patients quit smoking.

We found a higher prevalence of joint manifestations and chronic skin disorders in smoking CD and UC patients. Moreover, we found smoking to be significantly more common in both CD and UC patients with joint manifestations. Current data on the association of smoking and EIMs are inconclusive. While some studies on risk factors for EIMs found smoking to be associated with EIMs in CD but not in UC patients,[11,17] other studies found an increased prevalence of ocular EIMs,[18] spondylarthropathy and cutaneous complications[18] in smoking UC patients. Two studies reported no association between smoking and EIMs in CD.[19,20] The strength of the present study is that we were able to focus on smoking and EIMs in IBD in three different cohorts, encompassing more than 4000 patients. This cohort corroborated previous results and provided further insight into several aspects of this association. For the first time, a dose– response relationship was suggested. We could not clearly identify an association with specific phenotypes of joint manifestations, however. Furthermore, our data allowed us to correct for possible confounders, such as disease severity and the previous use of biologicals or immunosuppressive drugs, which had not been evaluated before.

The diverse effects of smoking on the clinical course in CD and UC are well established in the literature,[9,10,21] but the underlying mechanisms are incompletely understood. In the multivariable analyses of the COIN data, smoking was an independent factor for the presence of EIMs in both CD and UC, irrespective of disease severity. Based on a predefined statistical significance level of $p < 0.05$, the analyses in the Groningen cohort could not confirm these results, probably due to a smaller number of patients.[22] The molecular mechanisms through which the association between smoking and EIMs are established in UC and CD might be based on different pathways. It has been postulated that the opposing effects of smoking on the alimentary tract can be explained by differential effects on dendritic cells.[23] Furthermore, in mice smoking is associated with intestinal barrier dysfunction in the small intestine, but not in the large intestine, indicating different responses in ileal and colonic epithelial cells.[24]

Apart from smoking, female gender, greater age and a low level of education were also associated with EIMs. Female gender and greater age were previously identified as risk factors for EIMs in IBD.[20] As for low educational level, this association has not been described before. It can be speculated that worse control of disease and/or other environmental factors are involved in these patients. Of note, smoking was associated with EIMs independently of educational level.

Smoking has been identified as one of the most important extrinsic factors for the development and severity of rheumatoid arthritis (RA).[25–27] The pathophysiology of RA in smokers is believed to include oxidative stress, systemic inflammation, autoantibody formation and epigenetic changes, such as DNA methylation.[28] Moreover, smoking has been reported to be the main predictor of severe extra-articular manifestations in RA, such as rheumatoid vasculitis, polyneuropathy and pleuritis.[29–32] Both in CD and in RA, smoking has been associated with a poor response to antitumour necrosis factor (TNF) treatment.[33–35] Smoking has also been linked to a more severe disease course in psoriasis,[36,37] which is thought to be caused by smoking-induced oxidative damage along with insufficient capacity of antioxidant mechanisms.[38] Similar pathways might underlie the association of smoking with EIMs in IBD, although at present this assumption cannot be substantiated.

Smoking cessation may be beneficial in IBD patients with EIMs, as in both the COIN cohort and the Groningen cohort we observed a rapid decrease in prevalence rates of EIMs after smoking cessation towards levels seen in never smokers. The beneficial effect of smoking cessation on the clinical course of disease in CD patients has been reported previously,[39] but its effect on EIMs has never been demonstrated before. Whether the relationship between smoking cessation and a decline of EIMs is causal cannot be deduced from our data.

Some aspects of our findings need consideration. The results of the COIN study are based on self-reported data, which could have led to over- or underreporting of actual EIMs. However, the internal validity of this study seems to be robust[13] and the accuracy of responses to health-related questionnaires from patients with IBD is generally high.[40] Moreover, the prevalences of EIMs in the COIN and Groningen cohorts were very similar (31.3% and 32.3% respectively), and our observations are in line with those described in the literature.[3–7,41] The JOINT cohort was designed to study different aspects of joint complaints in IBD. Therefore, selection bias might have occurred in this cohort. For this reason, we analysed the results of this study separately and refrained from comparing the presence of skin disorders or eye diseases between smokers and non-smokers. Recall bias may be present for the number of pack-years per patient in the Groningen cohort. Self-reported smoking behaviour, however, has been rated as reliable in the literature, although in some studies a trend towards underestimation of total smoke exposure has been found.[42,43] A relatively small number (95) of currently smoking patients adequately reported their exact total smoke exposure. In a larger cohort, a dose–response relationship regarding smoking and EIMs might have reached statistical significance, but for now only a statistically significant trend could be detected in CD patients. Finally, the three examined studies differed in their baseline characteristics and definitions of EIMs. For example, the number of currently smoking CD patients was highest in the Groningen cohort, the mean age of all patients was highest in the COIN cohort, and the JOINT cohort had a relatively high number of anti-TNFα users. EIMs were collected by self-report in the COIN study, extracted from medical records in the Groningen study and objectified by an extensive medical assessment in the

JOINT study. However, regard-less of the differences between the cohorts, the analyses of all cohorts separately led to the same conclusion with respect to the association between smoking and EIMs in IBD.

In conclusion, we have demonstrated a positive association between smoking and EIMs in IBD in three different cohorts, in both CD and UC patients. Our data suggest a dose–response relation-ship regarding smoking behaviour. Most importantly, the prevalence of EIMs rapidly decreases towards levels found in never-smoking patients after smoking cessation. As EIMs frequently complicate the clinical course of IBD, clinicians should be aware that smoking cessation might reduce the burden of EIMs in these patients.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Univariable and multivariable analysis for the presence of EIMs in IBD (COIN cohort)

		EIMs	No EIMs	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Crohn's	Currently smoking vs. never smoking, n (%)	140 (25.8)	189 (18.6)	1.72 (1.32 – 2.25)	1.52 (1.15 – 2.01)*
	Ex-smoking vs. never smoking, n (%)	167 (37.3)	235 (30.1)	1.38 (1.08 – 1.76)	1.19 (0.92 – 1.54)
	Female gender (n, %)	367 (67.7)	617 (60.7)	1.36 (1.09 – 1.69)	1.51 (1.20 – 1.92)*
	Age – years, mean (SD)	49.9 (13.2)	45.3 (13.7)	1.03 (1.02 – 1.03)	1.03 (1.02 – 1.04)*
	Low education, n (%)	387 (71.4)	621 (61.1)	1.59 (1.27 – 2.00)	1.29 (1.01 – 1.63)*
	Disease duration, median (IQR)	18.0 (10.0 – 27.9)	14.0 (6.9 – 24.0)	1.02 (1.01 – 1.03)	1.01 (1.00 – 1.02)
	Current flare, n (%)	100 (18.5)	128 (12.6)	1.57 (1.20 – 2.09)	1.47 (1.09 – 1.97)*
	Previous use of Anti-TNF alpha, n (%)	193 (35.6)	287 (28.2)	1.41 (1.12 – 1.76)	1.63 (1.28 – 2.07)*
	Previous use of immunosuppressive drugs, n (%)	337 (62.2)	604 (59.4)	1.12 (0.91 – 1.39)	-
	Colonic disease vs. extra-colonic disease, n (%)	427 (80.9)	772 (79.0)	1.12 (0.86 – 1.47)	-
Ulcerative colitis	Currently smoking vs. never smoking, n (%)	32 (11.3)	63 (8.2)	1.74 (1.09 – 2.78)	1.75 (1.07 – 2.84)*
	Ex-smoking vs. never smoking, n (%)	115 (32.1)	136 (22.6)	1.63 (1.21 – 2.19)	1.41 (1.03 – 1.92)*
	Female gender (n, %)	163 (57.6)	365 (47.2)	1.52 (1.15 – 2.00)	2.11 (1.56 – 2.85)*
	Age – years, mean (SD)	53.3 (12.6)	47.7 (13.3)	1.03 (1.02 – 1.05)	1.04 (1.03 – 1.05)*
	Low education, n (%)	177 (62.5)	438 (56.7)	1.28 (0.97 – 1.69)	-
	Disease duration, median (IQR)	13.9 (7.0– 21.9)	11.9 (6.0– 20.9)	1.02 (1.00 – 1.03)	1.01 (0.99 – 1.02)
	Current flare, n (%)	47 (16.6)	126 (16.3)	1.02 (0.71 – 1.48)	0.98 (0.67 – 1.44)
	Previous use of Anti-TNF alpha, n (%)	28 (9.9)	63 (8.2)	1.24 (0.78 – 1.98)	-
	Previous use of immunosuppressive drugs, n (%)	100 (35.3)	262 (33.9)	1.07 (0.80 – 1.42)	-

SD: standard deviation; IQR: interquartile range; EIMs: extra-intestinal manifestations; OR: odds ratio; CI: confidence interval; *: p<0.05.

Supplementary Table 2. Univariable and multivariable analysis for the presence of EIMs in IBD (Groningen-cohort)

		EIMs	No EIMs	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Crohn's	Currently smoking vs. never smoking, n (%)	64 (37.0)	72 (29.6)	1.41 (0.87 – 2.30)	1.19 (0.65 – 2.19)
	Ex-smoking vs. never smoking, n (%)	58 (53.2)	89 (52.4)	1.04 (0.64 – 1.68)	-
	Female gender (n, %)	93 (70.5)	108 (61.4)	1.50 (0.93 – 2.43)	1.60 (0.83 – 3.08)
	Age – years, mean (SD)	41.0 (14.0)	39.0 (14.0)	1.01 (0.99 – 1.03)	-
	Low education, n (%)	74 (56.9)	88 (52.1)	1.31 (0.82 – 2.10)	-
	Disease duration, median (IQR)	10.0 (4.0–16.0)	9.0 (4.0–14.0)	1.01 (0.98 – 1.04)	-
	Current use of Anti-TNF alpha, n (%)	50 (38.5)	64 (39.8)	0.93 (0.58 – 1.52)	-
	Current use of immunosuppressive drugs, n (%)	71 (54.6)	84 (52.2)	1.13 (0.71 – 1.82)	-
	Colonic disease vs. extra-colonic disease, n (%)	93 (83.0)	114 (69.9)	2.10 (1.16 – 3.82)	1.41 (0.69 – 2.87)
Ulcerative colitis	Currently smoking vs. never smoking, n (%)	9 (14.5)	26 (11.8)	1.42 (0.60 – 3.39)	-
	Ex-smoking vs. never smoking, n (%)	26 (49.1)	88 (44.2)	1.22 (0.66 – 2.23)	-
	Female gender (n, %)	16 (34.8)	45 (30.2)	1.47 (0.76 – 2.85)	-
	Age – years, mean (SD)	44.0 (13.0)	42.0 (15.0)	1.00 (0.98 – 1.03)	-
	Low education, n (%)	32 (68.1)	77 (49.7)	2.31 (1.14 – 4.70)	2.31 (1.14 – 4.70)*
	Disease duration, median (IQR)	8.0 (4.0 – 18.0)	7.0 (4.0–11.0)	1.03 (0.99 – 1.07)	-
	Severe ulcerative colitis, n (%)	8 (38.1)	21 (25.9)	1 1.76 (0.64 – 4.83)	-
	Current use of Anti-TNF alpha, n (%)	3 (6.5)	7 (4.7)	1.27 (0.31 – 5.25)	-
	Current use of immunosuppressive drugs, n (%)	16 (34.8)	45 (30.2)	1.30 (0.63 – 2.66)	-

SD: standard deviation; IQR: interquartile range; EIMs: extra-intestinal manifestations; OR: odds ratio; CI: confidence interval. *: p<0.05

CHAPTER 3.2

Smoking is associated with higher disease-related costs and lower 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 more than 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.

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 health-care and societal perspectives.

MATERIALS AND METHODS

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

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]

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.

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.

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 1.[2,19–21] Healthcare costs consisted of medication use, hospital admissions, surgeries, diagnostic procedures and out-patient 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 (e.g. shopping, house-work, 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, i.e. 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).

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).

RESULTS

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 2. 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%, $p = 0.02$).

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), $p < 0.01$) (Fig. 1; Supplementary Table 3). 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 (Fig. 1; Supplementary table 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 (i.e. gender, age, employment status, education level) and disease-specific parameters (flares and previous abdominal surgery), current smoking (as compared with never smoking)

Table 1. Baseline characteristics

	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	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

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) (Fig. 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

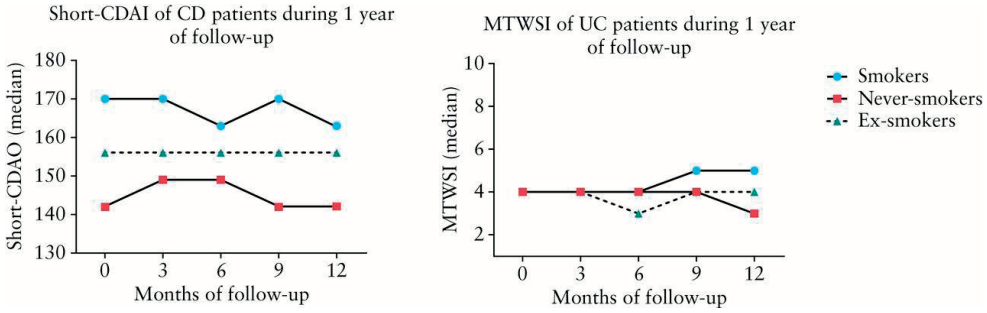

Fig.1: Comparison of disease activity scores of smokers, ex-smokers and non-smokers over 1 year of follow-up

Table 2. Comparison of disease course between smokers, ex-smokers and non-smokers

	10% highest societal costs			10% highest healthcare costs		
Characteristics	**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.

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 (Supplementary Table 3). In our sensitivity analysis, calculated annual costs (i.e. healthcare, patient, societal) were comparable to multiple imputed data, except for productivity losses (Supplementary Table 4).

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).

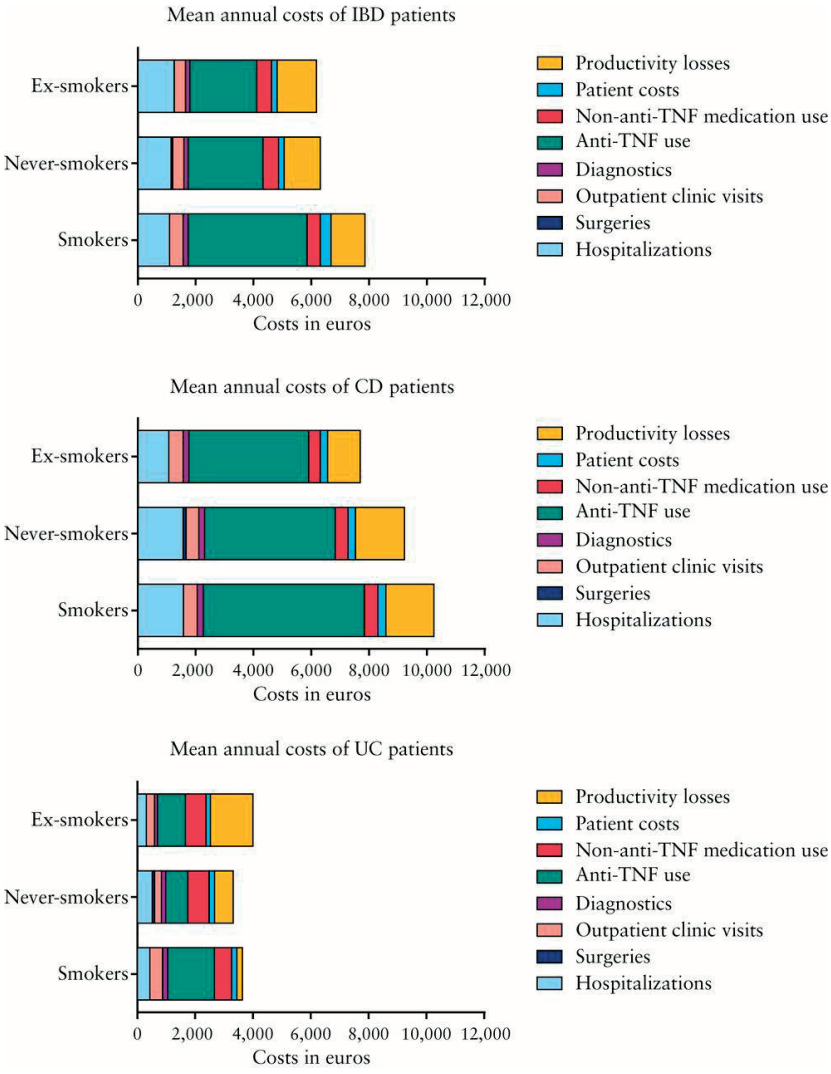

Fig.2: Costs of smokers, never-smokers and ex-smokers

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 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 5). In CD patients who quitted smoking within 5 years before inclusion, anti-TNF compounds were more frequently

Table 3. Costs of smokers, never-smokers and ex-smokers

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]

prescribed than in patients who quit smoking longer than 5 years previously (34.4% vs 19.1%, p < 0.01) (Supplementary Table 6). 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).

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

	10% highest annual societal costs			10% highest annual healthcare costs		
Characteristics	**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.

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).

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 (Fig. 3, Supplementary Table 7). 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 (Fig. 3, Supplementary Table 7).

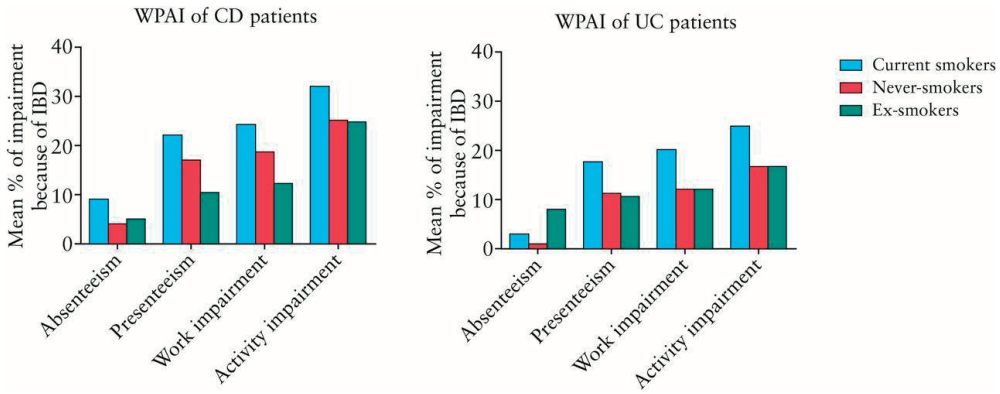

Fig.3: Percentages of impairment in work productivity and daily activities because of IBD of smokers, never-smokers and ex-smokers

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.

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 8). Further specified, median IBDQ scores 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) (Fig. 4; Supplementary Table 9).

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 10). 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 (Fig. 4; Supplementary Table 10). 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.

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 11).

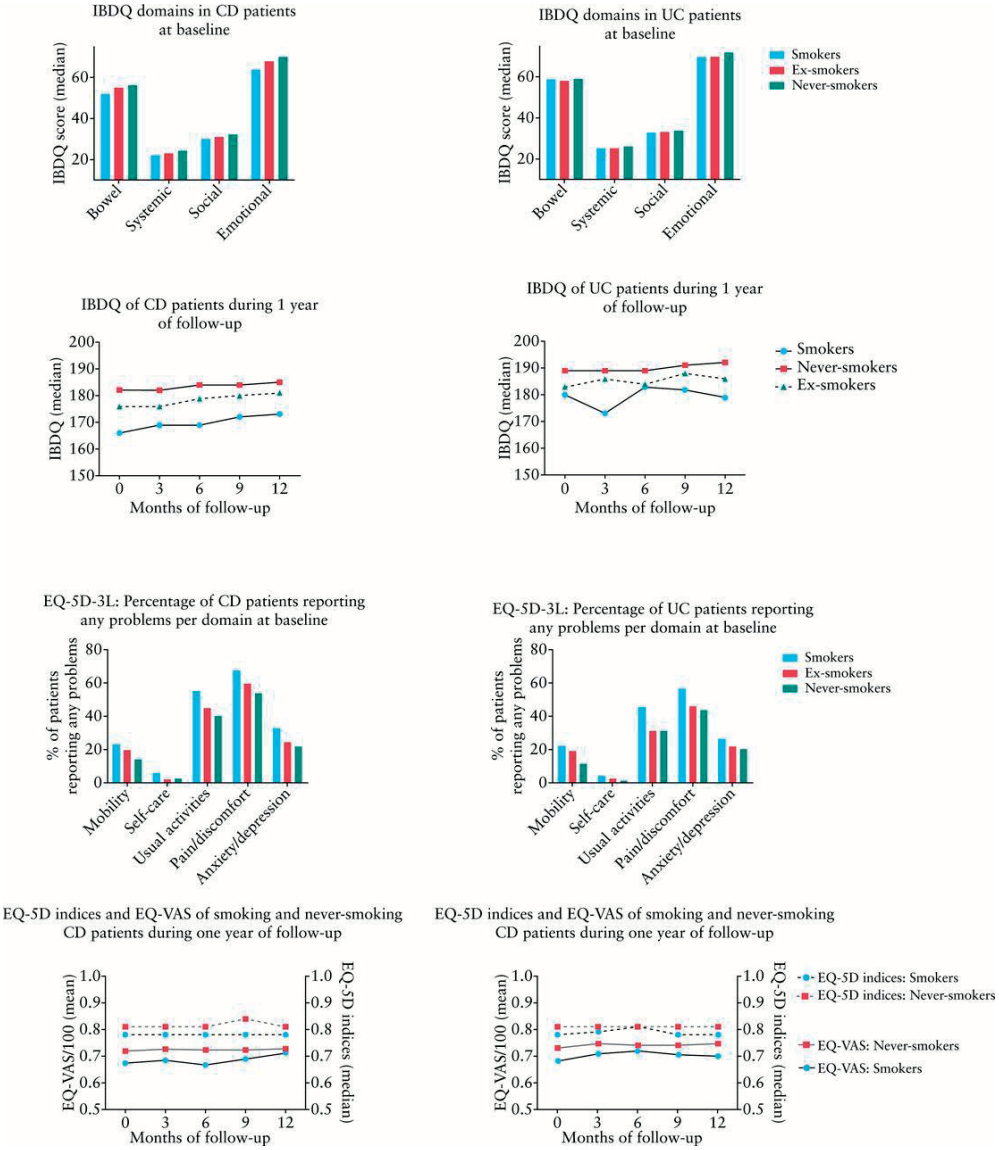

Fig.4: The quality of life of smoking, never-smoking and ex-smoking IBD patients

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, 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 health-care 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 program for CD patients, using a Markov model, was published.[39] The perspective was the publicly funded healthcare system. All strategies (i.e. counselling, nicotine replacement therapy, nicotine replacement therapy + counselling, and Varenicline) were dominant (cost saving) over a strategy with no program. The economic consequences of smoking in CD, as presented in our study, underscore this need for smoking cessation programs. In clinical practice, a successful smoking cessation program 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 health care. 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 com-pared 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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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Unit prices of resource use, expressed in 2014 euros*

	Unit price (€) Cost price per visit	**References**
Outpatient clinic consultations		
District hospital	68.52	(1)
University medical centre	138.11	(1)
Emergency room	161.66	(1)
General practitioner		(1)
Visit (day-time)	29.98	(1)
Home visit (day-time)	46.04	(1)
Visit (weekend/ night-time)	86.92[a]	(1)
Home visit (weekend/ night-time)	130.38[a]	(1)
	Cost price per hour	
IBD or stoma nurse – per hour	47.17	(1)
Dietician – per hour	51.62	(1)
Hospitalisation	Cost price per day	
Medical ward		
General hospital	465.71	(1)
University medical centre	615.60	(1)
Intensive care unit	2337.12	(1)
Medication use	Costs per 3 months	
Mesalazine	UC: 225.17[b]	(2)
	CD: 261.71[c]	(2)
Prednisone	16.00 [d]	(2)
Budesonide	201.20[e]	(2)
Azathioprine - 150 g/day	96.06[f]	(2)
Mercaptopurine - 50 mg/day	96.06[g]	(2)
Methotrexate - 15 mg/ week	263.35[h]	(2)
Infliximab	5,144.18[i]	(2)

	Unit price (€)		References
Adalimumab	4,625.84[j]		(2)
Surgery	Cost price per type of surgery [k]		
Ileocecal resection/ resection neoterminal ileum	1,255.04		(3)
Partial colectomy	1,829.00		(3)
Subtotal colectomy	1,829.00		(3)
Abcess surgery	178.08		(3)
Complex fistula surgery	2,440.12		(3)
Rectum amputation	3,337.94		(3)
Ileostomy	787.58		(3)
Diagnostic procedures	Cost price per type of diagnostic procedure		
Colonoscopy	364.42		(3)
CT scan	162.14		(3)
MRI scan	199.24		(3)
Abdominal X-ray	45.98		(3)
Ultrasonography	39.93		(3)
DXA scan	89.54		(3)
Laboratory	19.14[l]		(3)
Sick leave from paid work	Productivity losses per working hour		
	Females	Males	
15-19 years	9.48	10.43	(1)
20-24 years	18.57	19.20	(1)
25-29 years	25.54	26.15	(1)
30-34 years	29.78	32.05	(1)
35-39 years	31.63	36.79	(1)
40-44 years	31.42	39.64	(1)
45-49 years	31.26	41.44	(1)
50-54 years	31.63	42.23	(1)
	Unit price	**(€)**	**References**
55-59 years	31.90	42.58	(1)
60-64 years	30.99	42.30	(1)

Sick leave from paid work (care-giver)	Productivity losses per working hour	
	32.98	(1)
Sick leave from unpaid work	Productivity losses per working hour	
	13.74	(1)

[a] Price based on average cost price of 55 general practitioners (weekend/evening/night).

[b] Price based on average dose of 2000 mg/day during 91 days.

[c] Price based on average dose of 2400 mg/day during 91 days.

[d] Price based on average dose of 10 mg/day during 91 days.

[e] Price based on average dose of 6 g/day during 91 days.

[f] Price based on average dose of 150 mg/day during 91 days.

[g] Price based on average dose of 50 mg/day during 91 days.

[h] Price based on average dose of 15 mg/ week during 13 weeks.

[i] Price based on average weight of 75 kg and 1.8 infusions per 3 months.

[j] Price based on 6,5 injections per 3 months (81% administered adalimumab 40 mgs per 2 weeks) or 13 injections per 3 months (19% of patients administered adalimumab 80 mgs per 2 weeks).

[k] Days admitted at the surgical or medical were not included in the cost price of surgery, but assessed separately .

[l] Price based on full blood count and differential, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, sodium, potassium, creatinine, albumin.

[m] For patients with an ileostomy costs for caring for the stoma were based on a standard care package. This is based on the assumption of an exchange of base disk 4 times per week and of the ileostomy bag twice/day.

[*] In 2014, 1€ was equal to 0.754 US$, or 0.814 US$ when using data on purchasing power parity (PPP)(23)

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Supplementary Table 2. Main characteristics of total study population

Characteristics	IBD (n = 3,030)	CD (n=1,558)	UC (n=1,054)	IBD-U (n=418)
Male gender (n, %)	1325 (43.7)	574 (36.8)	527 (50.0)	224 (53.6)
Age – years (mean, SD)	48.2 (13.6)	46.9 (13.7)	49.2 (13.3)	50.4 (13.8)
Disease duration – years (median, IQR)	13.9 (6.8 – 23.0)	15.3 (7.9 – 25.8)	12.8 (6.2 – 20.9)	11.8 (5.0 – 22.0)
Smoking (n, %)				
Current	486 (16.0)	329 (21.1)	95 (9.0)	62 (14.8)
Never	1605 (53.0)	781 (50.1)	603 (57.1)	221 (53.1)
Ex-smoker	939 (31.0)	448 (28.8)	358 (33.9)	133 (32.0)
Disease localization, n (%)				
Colon	1740 (57.4)	431 (27.7)	1014 (96.2)	295 (70.6)
Small intestine	341 (11.3)	306 (19.6)	0 (0.0)	35 (8.4)
Both colon and small intestine	833 (27.5)	768 (49.3)	0 (0.0)	65 (15.6)
Unknown	116 (3.8)	53 (3.4)	40 (3.8)	23 (5.5%)
Disease in remission, n (%)	2549 (84.2)	1329 (85.4)	881 (83.6)	339 (81.1)
Stoma, n (%)	300 (9.9)	192 (12.3)	61 (5.8)	47 (11.2)
Pouch n (%)	167 (5.5)	28 (1.8)	94 (8.9)	45 (10.8)
Fistula, n (%)	268 (8.8)	220 (14.1)	0.0 (0%)	48 (11.5)
Abdominal surgery in the past, n (%)	1143 (37.7)	843 (54.1)	194 (18.4)	106 (25.4)
Low education, n (%)	1898 (62.6)	1008 (64.7)	614 (58.3)	276 (66.0)
Currently employed, n (%)	1557 (51.4)	738 (47.4)	614 (58.3)	205 (49.0)

IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis, IBD-U: IBD- Unknown; SD: standard deviation; IQR: interquartile range.

Supplementary Table 3. Comparison of disease activity scores of smokers, ex-smokers and never- smokers over one year of follow-up

Median (IQR)	**1.Current smokers**	**2.Never-smokers**	**3.Ex-smokers**	**P- value (1 vs. 2)**	**P-value (1 vs. 3)**
		Crohn's disease- short-CDAI			
Baseline	170 (128 – 219)	142 (114 – 177)	156 (114 – 198)	<0.01	<0.01
3 months	170 (128 – 212)	149 (114 – 177)	156 (121 – 191)	<0.01	<0.01
6 months	163 (128 – 205)	149 (114 – 177)	156 (114 – 202)	<0.01	0.12
9 months	170 (128 – 212)	142 (114 – 177)	156 (114 – 191)	<0.01	0.01
12 months	163 (128 – 205)	142 (114 – 184)	156 (114 – 198)	<0.01	0.06
		Ulcerative colitis – MTWSI			
Baseline	4 (2 -6)	4 (2 – 6)	4 (2 – 6)	0.50	0.91
3 months	4 (2 – 7)	4 (2 – 6)	4 (2 – 6)	0.08	0.21
6 months	4 (3 – 7)	4 (2 – 6)	3 (2 – 6)	0.24	0.13
9 months	5 (3 – 7)	4 (2 – 6)	4 (2 – 6)	<0.05	0.03
12 months	5 (2 – 7)	3 (2 – 6)	4 (2 – 6)	0.04	0.32

CDAI: Crohn's disease activity index; MTWSI: Modified Truelove and Witts index; IQR: interquartile range

Supplementary Table 4. Pooled total costs of five imputations, 2014 euros

Mean	**Smokers**	**Never-smokers**	**Ex-smokers**
		Inflammatory Bowel Disease	
Healthcare costs	5,465	4,611	4,491
Patient costs	278	232	295
Productivity losses	1,324	1,370	1,478
Societal costs	**7,067**	**6,212**	**6,264**
		Crohn's disease	
Healthcare costs	6,536	6,109	5,996
Patient costs	255	247	401
Productivity losses	1,359	1,625	1,352
Societal costs	**8,151**	**7,981**	**7,749**
		Ulcerative colitis	
Healthcare costs	3,511	3,175	3,319
Patient costs	213	205	194
Productivity losses	1,379	993	1,605
Societal costs	**5,103**	**4,373**	**5,118**

Supplementary Table 5. Costs of ex-smokers during one year of follow-up, expressed in 2014 euros*

Mean + 95% CI	**Quit smoking ≤ 5 years**	**Quit smoking > 5 years**	**P-value**
Inflammatory Bowel Disease	*n =64*	*n =315*	
Healthcare costs	6,742 (4,371 – 9,256)	3,737 (3,032 – 4,601)	0.01
Patient costs	162 (89 – 258)	201 (162 – 251)	0.48
Productivity losses	2,437 (856 – 4,758)	1,196 (582 – 1,920)	0.16
Societal costs	**9,342 (6,010 –12,788)**	**5,135 (4,122 – 6,303)**	**0.01**
Crohn's disease	*n =39*	*n =124*	
Healthcare costs	9,552 (6,169 – 12,978)	6,158 (4,603 – 7,908)	0.07
Patient costs	144 (75 – 225)	259 (171 – 378)	0.23
Productivity losses	2,211 (587 – 4,470)	861 (224 – 1,916)	0.16
Societal costs	**11,907 (7,433 –16,559)**	**7,276 (5,401 – 9,471)**	**<0.05**
Ulcerative colitis	*n =20*	*n =138*	
Healthcare costs	1,887 (652 – 4,462)	2,518 (1,809 – 3,386)	0.59
Patient costs	52 (18 – 100)	167 (121 – 224)	0.08
Productivity losses	2,802 (10 – 8,301)	1,347 (402 – 2,584)	0.39
Societal costs	**4,740 (984 – 10,372)**	**4,031 (2,791 – 5,816)**	**0.76**

CI: Confidence interval

* In 2014, 1€ was equal to 0.754 US$, or 0.814 US$ when using data on purchasing power parity (PPP)(23)

Supplementary Table 6. Disease course of ex-smokers at baseline

Parameter	**Quit smoking ≤ 5 years**	**Quit smoking > 5 years**	**P-value**
Crohn's disease	*n = 121*	*n =310*	
Flare, n (%)	19 (15.7)	45 (14.4)	0.74
Fistula, n (%)	17 (14.0)	42 (13.5)	0.87
Medication use, n (%)*	68 (73.1)	202 (75.9)	0.59
5-ASA	12 (12.9)	77 (28.8)	<0.01
Steroids	3 (3.2)	17 (6.4)	0.26
Anti-TNF	32 (34.4)	51 (19.1)	<0.01
Immunosuppressive drugs (Aza/6MP/MTX)	30 (32.3)	80 (30.0)	0.68
Short-CDAI, median (IQR)	142 (121 – 191)	156 (114 – 198)	0.40
Ulcerative colitis	*n = 69*	*n =405*	
Flare, n (%)	14 (20.3)	83 (20.6)	0.95
Medication use, n (%)*	42 (76.4)	272 (76.8)	0.94
5-ASA	35 (63.6)	222 (62.5)	0.88
Steroids	1 (1.8)	26 (7.3)	0.13
Anti-TNF	3 (5.5)	18 (5.1)	0.90
Immunosuppressive drugs (Aza/6MP/MTX)	14 (25.5)	60 (16.9)	0.13
MTWSI, median (IQR)	4 (3 – 6)	4 (2 – 7)	0.90

*After 3 months of follow-up; ASA: aminosalicylic acid; Aza: azathioprine; 6MP: 6-mercaptopurine; MTX: methotrexate; TNF: tumor necrosis factor; IQR: Interquartile range; CDAI: Crohn's disease activity index; MTWSI: Modified Truelove and Witts Index

Supplementary Table 7. Work Productivity and Activity Impairment of smokers, never-smokers and ex- smokers

Mean % (SD)	**1.Current smokers**	**2.Never-smokers**	**3.Ex-smokers**	**P- value (1 vs. 2)**	**P-value (1 vs. 3)**
		Crohn's disease			
Absenteeism	9.0 (24.0)	4.1 (14.7)	5.1 (19.2)	0.04	0.24
Presenteeism	22.1 (22.3)	17.0 (21.6)	10.5 (14.8)	0.09	<0.01
Work impairment	24.2 (25.2)	18.8 (24.1)	12.2 (17.3)	0.11	<0.01
Activity impairment	32.0 (27.4)	25.1 (26.4)	24.9 (26.7)	0.01	0.01
		Ulcerative colitis			
Absenteeism	2.9 (10.7)	1.0 (5.4)	8.0 (24.8)	0.13	0.32
Presenteeism	17.6 (21.1)	11.4 (16.7)	10.7 (18.1)	0.09	0.11
Work impairment	20.1 (22.8)	12.1 (17.8)	12.2 (10.2)	0.04	0.10
Activity impairment	24.9 (28.6)	16.8 (22.1)	16.7 (23.1)	0.03	0.04

SD: Standard deviation

Supplementary Table 8. Multivariate analysis for the 10% lowest IBDQ-scores at baseline

Characteristics	Unadjusted OR (95%CI)	Adjusted OR* (95% CI)	P-value
Crohn's disease (n=1,558)			
Current smoking (vs. never- smoking)	2.17 (1.44 – 3.26)	1.54 (0.93 – 2.56)	0.09
Ex-smoking (vs. never- smoking)	1.63 (1.10 – 2.43)	1.21 (0.73 – 2.01)	0.46
Female gender (vs. male gender)	1.35 (0.95 – 1.93)	1.03 (0.65 – 1.63)	0.91
Age (per year)	0.99 (0.98 – 1.01)	0.98 (0.96 – 1.00)	0.06
Disease duration (per year)	0.99 (0.98 – 1.01)	-	-
Low education (vs. high education)	2.09 (1.41 – 3.10)	1.61 (0.98 – 2.65)	0.06
Currently employed (vs. currently unemployed)	0.17 (0.11 – 0.25)	0.18 (0.11 – 0.29)	<0.01
Current flare (vs. current remission)	6.40 (4.48 – 9.14)	5.41 (3.51 – 8.33)	<0.01
Ulcerative colitis (n=1,056)			
Current smoking (vs. never- smoking)	1.60 (1.05 – 2.43)	1.55 (0.88 – 2.72)	0.13
Ex-smoking (vs. never- smoking)	1.39 (0.70 – 2.77)	1.12 (0.47 – 2.68)	0.80
Female gender (vs. male gender)	2.13 (1.41 – 3.23)	1.77 (1.03 – 3.01)	0.04
Age (per year)	0.98 (0.97 – 1.00)	0.97 (0.95 – 1.00)	0.03
Disease duration (per year)	0.98 (0.96 – 1.00)	0.98 (0.95 – 1.01)	0.25
Low education (vs. high education)	1.78 (1.54 – 2.71)	1.96 (1.13 – 3.38)	0.02
Currently employed (vs. currently unemployed)	0.30 (0.19 – 0.49)	0.19 (0.10 – 0.34)	<0.01
Current flare (vs. current remission)	8.06 (5.29 – 12.29)	9.97 (5.82 – 17.10)	<0.01

OR: Odds ratio; CI: Confidence interval. *Variables with a p-value <0.10 were incorporated in the multivariate analysis

Supplementary Table 9. IBDQ-scores of smoking, never-smoking and ex-smoking patients at baseline and during follow-up

		1.Current smokers	2.Never-smokers	3.Ex-smokers	P- value (1 vs. 2)	P- value (1 vs. 3)
Crohn's disease	*IBDQ domains at baseline, median (IQR)*					
	Bowel	52 (45 – 59)	56 (49 – 63)	55 (48 – 61)	<0.01	<0.01
	Systemic	22 (17 – 26)	24 (20 – 29)	23 (18 – 27)	<0.01	<0.01
	Social	30 (23 – 34)	32 (27 – 35)	31 (18 – 27)	<0.01	0.01
	Emotional	64 (54 – 72)	70 (61 – 76)	68 (60 – 75)	<0.01	<0.01
	Total IBDQ scores during follow-up, median (IQR)					
	Baseline	166 (143 – 188)	182 (158 – 199)	176 (153 – 196)	<0.01	<0.01
	3months	169 (145 – 190)	182 (158 – 199)	176 (156 – 196)	<0.01	0.01
	6months	169 (148 – 191)	184 (160 – 199)	179 (156 – 198)	<0.01	0.01
	9months	172 (153 – 191)	184 (160 – 200)	180 (154 – 198)	<0.01	0.02
	12months	173 (147 – 192)	185 (162 – 199)	181 (160 – 196)	<0.01	0.02
Ulcerative colitis	*IBDQ domains at baseline, median (IQR)*					
	Bowel	59 (51 – 64)	59 (52 – 65)	58 (50 – 64)	0.46	0.79
	Systemic	25 (19 – 28)	26 (22 – 30)	25 (20 – 29)	<0.01	0.28
	Social	33 (27 – 35)	34 (29 – 35)	33 (28 – 35)	0.24	0.58
	Emotional	70 (57 – 75)	72 (62 – 77)	70 (59 – 77)	0.09	0.73
	Total IBDQ scores during follow-up, median (IQR)					
	Baseline	182 (157 – 199)	190 (165 – 204)	185 (161 – 202)	0.06	0.71
	3months	174 (155 – 201)	189 (168 – 204)	188 (167 – 202)	0.02	0.10
	6months	179 (158 – 198)	192 (170 – 205)	189 (167 – 204)	0.02	0.07
	9months	174 (141 – 193)	192 (170 – 205)	191 (168 – 204)	0.01	0.01
	12months	180 (156 – 202)	194 (171 – 206)	188 (165 – 204)	<0.01	0.08

IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: Interquartile Range

Supplementary Table 10. Generic HrQoL of smoking, never smoking and ex-smoking patients at baseline and during follow-up, using the EQ-5D-3L instrument

		1.Current smokers	2.Never-smokers	3.Ex-smokers	P- value (1 vs. 2)	P- value (1 vs. 3)
Crohn's disease	*Profile of the population at baseline: % of patients reporting any problems per dimension*					
	Mobility	23.1	14.0	19.8	<0.01	0.24
	Self-care	5.8	2.6	2.2	0.01	0.01
	Usual activities	55.3	40.1	45.1	<0.01	0.01
	Pain/discomfort	67.5	53.9	59.4	<0.01	0.02
	Anxiety/depression	32.8	22.0	24.3	<0.01	0.01
	EQ-VAS scores, mean (SD)					
	Baseline	67.4 (16.1)	71.9 (13.3)	69.9 (14.5)	<0.01	0.02
	3months	68.4 (16.7)	72.6 (14.5)	71.3 (14.5)	<0.01	0.02
	6months	66.8 (18.6)	72.2 (16.0)	70.5 (16.3)	<0.01	0.03
	9months	69.0 (16.0)	72.2 (16.0)	71.3 (14.7)	0.03	0.13
	12months	71.1 (14.6)	72.8 (15.6)	71.6 (16.6)	0.20	0.71
	EQ-indices, median (IQR)					
	Baseline	0.78 (0.68 – 0.81)	0.81 (0.69 – 0.84)	0.81 (0.69 – 0.84)	<0.01	0.01
	3months	0.78 (0.68 – 0.81)	0.81 (0.69 – 0.84)	0.78 (0.69 – 0.84)	0.02	0.16
	6months	0.78 (0.69 – 0.81)	0.81 (0.69 – 0.84)	0.78 (0.69 – 0.84)	0.01	0.09
	9months	0.78 (0.69 – 0.84)	0.84 (0.69 – 0.84)	0.81 (0.72 – 0.84)	0.09	0.01
	12months	0.78 (0.69 – 0.81)	0.81 (0.69 – 0.84)	0.78 (0.69 – 0.81)	0.02	0.24
Crohn's disease	*Profile of the population at baseline: % of patients reporting any problems per dimension*					
	Mobility	22.1	11.4	19.0	<0.01	0.50
	Self-care	4.2	1.2	2.5	0.03	0.38
	Usual activities	45.3	31.0	31.0	0.01	0.01
	Pain/discomfort	56.8	43.6	45.8	0.02	0.06
	Anxiety/depression	26.3	20.1	21.8	0.16	0.35
	EQ-VAS scores, mean (SD)					
	Baseline	69.0 (15.2)	73.6 (14.0)	72.8 (13.0)	<0.01	0.02
	3months	70.7 (15.8)	75.5 (13.3)	74.5 (14.0)	0.01	0.04
	6months	72.3 (14.8)	75.0 (16.4)	74.4 (15.4)	0.24	0.34
	9months	69.5 (15.4)	74.3 (16.3)	73.9 (15.0)	0.06	0.07
	12months	71.9 (13.8)	75.3 (17.0)	73.3 (17.4)	0.15	0.58
	EQ-indices, median (IQR)					
	Baseline	0.78 (0.69 – 0.81)	0.81 (0.72 – 0.84)	0.81 (0.69 – 0.84)	0.05	0.43
	3months	0.81 (0.69 – 0.81)	0.81 (0.72 – 0.84)	0.81 (0.72 – 0.84)	0.09	0.08
	6months	0.81 (0.65 – 0.81)	0.81 (0.72 – 0.84)	0.81 (0.74 – 0.84)	0.02	0.02
	9months	0.78 (0.65 – 0.81)	0.81 (0.72 – 0.84)	0.81 (0.69 – 0.84)	0.03	0.08
	12months	0.78 (0.69 – 0.81)	0.81 (0.71 – 0.84)	0.78 (0.69 – 0.81)	0.03	0.39

SD: Standard deviation; IQR: Interquartile range: EQ: Euroqol; VAS: Visual Analogue Scale

Supplementary Table 11. Health-related quality-of-life of ex-smokers at baseline

Quality of life instrument	**Quit smoking ≤ 5 years**	**Quit smoking > 5 years**	**P-value**
Crohn's disease	*n = 121*	*n =310*	
IBDQ, median (IQR)	176 (148 – 196)	176 (156 – 196)	0.58
EQ-5D-3L, % of patients with any problems per dimension			
Mobility	19.8	20.2	0.93
Self-care	1.7	2.6	0.57
Usual activities	49.6	44.2	0.32
Pain/discomfort	54.5	61.9	0.16
Anxiety/depression	24.0	25.0	0.82
EQ-VAS, mean (SD)	70.4 (15.4)	69.8 (13.9)	0.74
EQ-Indices, median (IQR)	0.78 (0.69 – 0.83)	0.81 (0.69 – 0.84)	0.80
Ulcerative colitis	*n = 69*	*n =405*	
IBDQ, median (IQR)	181 (160 – 197)	181 (160 – 202)	0.54
EQ-5D-3L, % of patients with any problems dimension			
Mobility	20.3	20.1	0.98
Self-care	5.8	2.2	0.09
Usual activities	43.5	32.9	0.09
Pain/discomfort	50.7	48.2	0.69
Anxiety/depression	26.1	21.6	0.41
EQ-VAS, mean (SD)	71.9 (12.2)	72.3 (13.2)	0.81
EQ-Indices, median (IQR)	0.78 (0.69 – 0.81)	0.81 (0.69 – 0.84)	0.17

IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: Interquartile Range, EQ-5D: Euroqol-5 Dimensions 3 Levels; EQ-Vas: Euroqol- Visual Analogue Scale; SD: standard deviation

CHAPTER 4

Burden of non-adherence on IBD

CHAPTER 4.I

Assessing medication adherence in inflammatory bowel disease using self-report: a comparison of tools

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ABSTRACT

Background: Capturing (non)-adherence to medical prescriptions in patients with inflammatory bowel disease (IBD) is challenging. We aimed to compare 3 different tools to measure self-assessed medication adherence of patients with IBD.

Methods: Adult patients with Crohn's disease and ulcerative colitis were prospectively followed. IBD-specific medication use was collected by 3-monthly questionnaires. At 2.5 years of follow-up, medication adherence was assessed using 3 tools: (1) the 8-item Morisky Medication Adherence Scale (MMAS-8), (2) the single question how well patients take their daily medication using a Visual Analogue Scale (VAS), and (3) the Forget Medicine scale (FM), assessing how often patients forget their medication. Cross-sectional agreement among measures was visualized with scatterplots and quantified with Spearman's rank correlations.

Results: In total, 913 patients with IBD were analyzed, 697 of whom received IBD-specific medication. High adherence on the MMAS-8 was consistent with high scores on the VAS and low scores on the FM. Disagreement between tools increased when patients were less adherent. A correlation of 0.44 was found between the MMAS-8 and VAS; 0.59 between the MMAS-8 and FM, and 0.55 between the VAS and FM (all $P < 0.01$). The VAS most optimally represented the quantitative variability of adherence, whereas the MMAS-8 and the FM might have resulted in overestimation or underestimation of adherence due to unequal differences in outcome possibilities.

Conclusions: In patients with IBD, a VAS seems the most appropriate tool for quantifying medication adherence in clinical practice. The MMAS-8 may be used additionally to provide insight in specific reasons for non-adherence.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic intestinal disorder. During the course of disease, several medical therapies are required to control flares and to maintain remission.[1] Non-adherence to medical therapy is a frequently encountered problem in the treatment of patients with IBD and is associated with an increased risk of active disease.[1,2] In other chronic diseases, such as rheumatoid arthritis and asthma, non-adherence to (maintenance) therapy has been equally linked to exacerbations of the disease course.[3,4]

Capturing non-adherence in daily practice remains a challenge. The most reliable approach would be to measure blood or urine levels (therapeutic drug monitoring), but this requires hospital visits and leads to increased healthcare costs. Counting rates of prescription refills may not cover the actual drug use of patients, and reports of clinicians may be unreliable.[5,6] Self-report can be considered the most accessible, inexpensive, and easy-to-use method to assess adherence to medical prescriptions. It is, however, presently unclear which tool provides the most reliable reflection of actual medication adherence.[7,8]

The aims of our study were to assess medication adherence using different tools in a large cohort of patients with IBD and to compare the outcomes with respect to reliability and applicability for the use in clinical practice.

METHODS

Ethical Considerations

This study was carried out with the approval of the Medical Ethics Committee of the University Medical Center Utrecht.

Patient Population and Study Design

The COIN study (Costs of Inflammatory Bowel Disease in the Netherlands)[9] is a prospective cohort study initiated in 2010 with the aim to study the costs and health-related quality of life among patients with IBD. The study population consists of adult patients with CD and UC from 7 university hospitals and 7 general hospitals. Eligible patients were invited to fill-out a Web-based baseline questionnaire (collecting data on demo-graphics, disease course, and health-related quality of life), followed by 3-monthly follow-up questionnaires on the course of disease, health-related quality of life, and IBD-specific healthcare utilization, including medication use. Detailed information on the design of the study has been reported previously.[9,10]

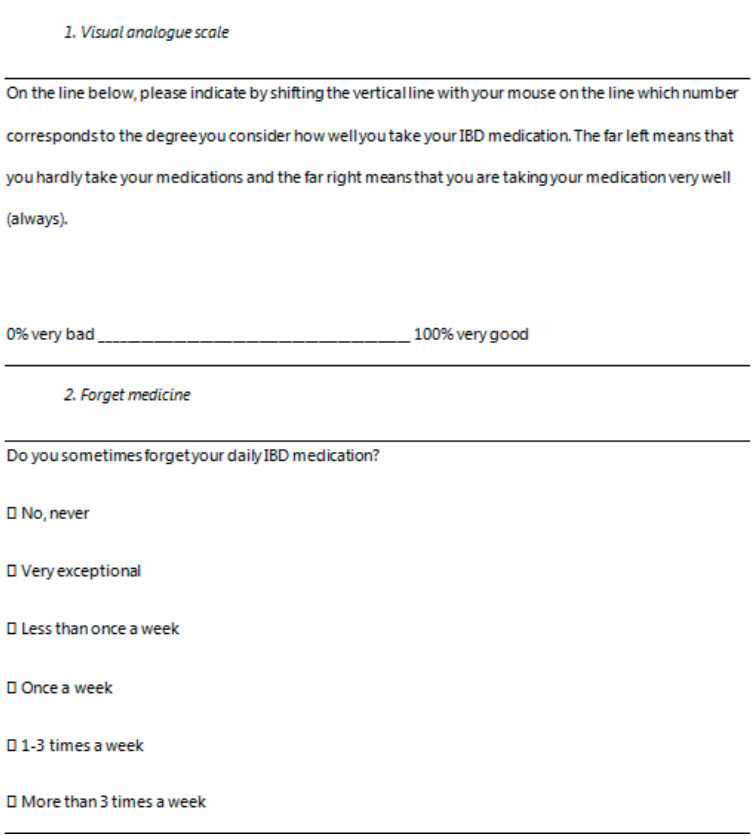
Measurement of Medication Adherence

At one time during follow-up (i.e., the tenth follow-up questionnaire; 2.5 years of follow-up), medication adherence was assessed using 3 different tools: (1) the validated 8-item Morisky Medication Adherence Scale (MMAS-8, including 8 questions covering various aspects of adherence behavior, with the possible answers “yes” and “no,” and higher total scores indicating a better adherence), for a specification of the MMAS-8 questionnaire, see reference [11,12] (2) the single question how well patients take their daily medication using a Visual Analogue Scale (VAS, ranging from 0 to 100, with 100 indicating a perfect adherence),[13,14] and (3) the Forget Medicine scale (FM), assessing how often patients forget to take their medicine (on a 6-point scale, with inclining rates of times patients forget their medicine). The VAS and the FM scale can be found in Fig.1.
For the MMAS-8, a total score of less than 6 is considered non-adherent, and for the VAS, a score of less than 80% is considered non-adherent.[15] As a undebated and accepted cutoff value has not yet been determined for the FM, we considered forgetting medication 1 to 3 times, or more frequently per week, non-adherent.

Statistical Analysis

Only patients who were currently taking IBD medication were included in the analyses. Distributions of medication adherence were described using medians, interquartile ranges,

and percentages of non-adherence. Agreement between the 3 scales was visualized with scatterplots and quantified with Spearman rank correlations.[16] In previous studies, younger age and current employment were consistent factors associated with non-adherence.5 To determine the representativeness of adherence outcomes in our cohort, we displayed non-adherence rates according to the 3 tools of different age and employment categories. P-values < 0.05 were considered statistical significant. Statistical analyses were performed with SPSS version 21 (IBM Corp., Armonk, NY).



1. Visual analogue scale

On the line below, please indicate by shifting the vertical line with your mouse on the line which number corresponds to the degree you consider how well you take your IBD medication. The far left means that you hardly take your medications and the far right means that you are taking your medication very well (always).

0% very bad _____ 100% very good

2. Forget medicine

Do you sometimes forget your daily IBD medication?

☐ No, never

☐ Very exceptional

☐ Less than once a week

☐ Once a week

☐ 1-3 times a week

☐ More than 3 times a week

Fig.1: the VAS and FM tool for measuring medication adherence in IBD

RESULTS

Patient Population

In total, 913 patients (462 CD, 335 UC, and 116 IBD-unknown) were analyzed, of whom 697 (77.1%) currently received medication for their IBD. Patients were assigned to "IBD-unknown" when they did not know their IBD subtype or reported UC with ileal involvement or fistulas. Patient characteristics and distributions of adherence measurements are shown in Table 1. Overall, patients who took IBD-specific medication re-ported a high median adherence (MMAS-8: 7.0 [interquartile range, 6.0–8.0]; VAS: 97% [interquartile range, 90–100]), and 54.2% of patients reported never to forget their IBD medication. The distribution of medication adherence scores did not differ between CD, UC, and IBD-unknown patients.

Table 1. Patient Characteristics and Distribution of Medication Adherence Among Study Participants

Characteristics	IBD (All) (n = 913)	CD (n = 462)	UC (n = 335)	IBD-unknown (n = 116)
Patient characteristics				
Male gender, n (%)	466 (51.0)	192 (41.6)	203 (60.6)	71 (61.2)
Age, mean (SD), yr	54.1 (13.4)	52.7 (13.8)	54.9 (12.9)	57.4 (12.7)
Low education, n (%)	546 (59.8)	285 (61.7)	186 (55.5)	75 (64.7)
Currently employed, n (%)	450 (72.7)	220 (66.3)	187 (81.3)	53 (74.6)
Disease duration, median (IQR)	18.9 (10.9–29.8)	19.9 (11.8–32.8)	17.8 (10.9–25.8)	18.3 (9.8–28.8)
Smoking, n (%)				
Current	130 (14.2)	88 (19.0)	25 (7.5)	17 (14.2)
Never	483 (52.9)	244 (52.8)	189 (56.4)	50 (43.1)
Ex-smoker	300 (32.9)	130 (28.1)	121 (36.1)	49 (42.2)
Current flare, n (%)	173 (19.1)	76 (16.6)	72 (21.7)	25 (21.7)
Medication use, n (%)	697 (77.1)	348 (75.8)	272 (82.2)	77 (67.5)
5-ASA	351 (38.4)	80 (17.3)	218 (65.1)	53 (45.7)
Steroids	64 (7.0)	41 (8.9)	16 (4.8)	7 (6.0)
Anti-TNF	135 (14.8)	110 (23.8)	20 (6.0)	5 (4.3)
Immunosuppressive drugs (AZA/6MP/MTX)	226 (24.8)	143 (31.0)	67 (20.0)	16 (13.8)
Distributions of medication adherence in patients taking IBDmedication				
MMAS-8, median (IQR)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)
VAS, median (IQR)	97 (90–100)	97 (92–100)	97 (89–99)	96 (86–100)
Do you sometimes forget your daily IBD medication? n (%)				
Never	371 (54.2)	191 (56.2)	138 (51.5)	42 (55.3)
Very exceptional	230 (33.6)	113 (33.2)	90 (33.6)	27 (35.5)
Less than once a week	44 (6.4)	20 (5.9)	21 (7.8)	3 (3.9)
Once a week	24 (3.5)	10 (2.9)	11 (4.1)	3 (3.9)
1–3 times a week	11 (1.6)	5 (1.5)	5 (1.9)	1 (1.3)
More than 3 times a week	4 (0.6)	1 (0.3)	3 (1.1)	4 (0.6)

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

Comparison of Non-adherence Rates and Associations Between Tools

High scores on the MMAS-8 were consistent with high scores on the VAS and low scores on the FM (Fig. 2). Disagreement between tools increased when patients had worse adherence scores. For example, when applying the clinical cutoffs of (non)-adherence, 78% of patients reported high adherence and 7% low adherence on both the VAS and the MMAS-8. However, 11% was categorized as low adherent on the MMAS-8 but high adherent on the VAS, whereas another 4% was high adherent on the MMAS-8 but low adherent on the VAS (Tables 2 and 3). A similar pattern for (dis)agreement was observed between the FM on one hand and the MMAS-8 and VAS on the other hand. The correlation was 0.44 between the MMAS-8 and VAS, 0.59 between the MMAS-8 and FM, and 0.55 between the VAS and FM (all $P < 0.01$) (Fig. 2).

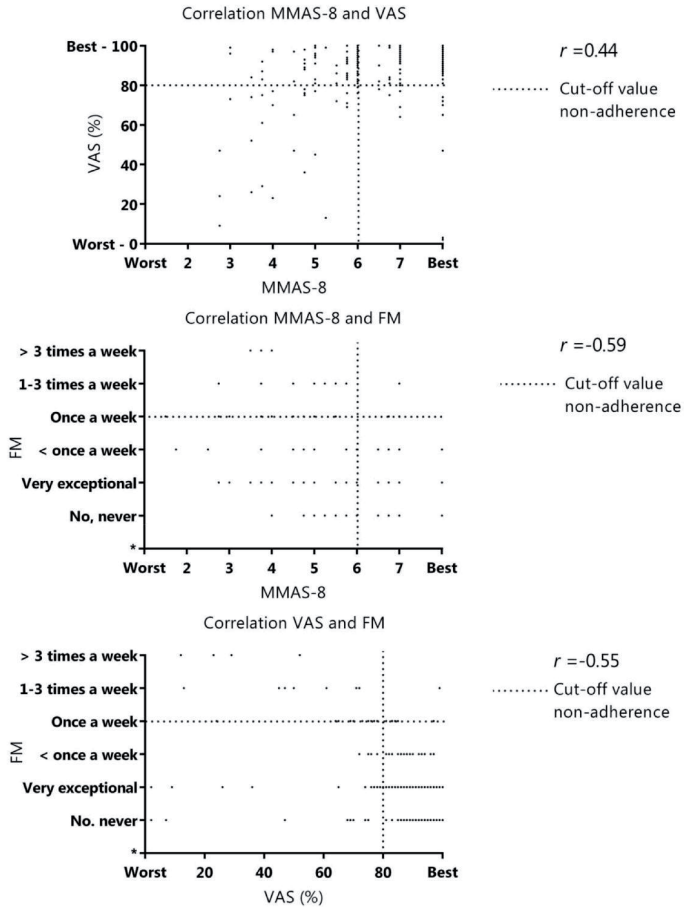


Fig.2: Associations of tools to measure medication adherence in patients with IBD.

Non-adherence in Age and Employment Categories

With the predetermined cutoff values, all 3 tools identified more young and employed patients as non-adherent, which proved to be statistically significant for age using the MMAS-8 (Table 4).

Table 2. Concordances of 3 Tools in Categorizing Non-adherence in Patients with IBD

	MMAS-8	
Concordance (%)	**Non-adherent**	**Adherent**
FM		
Non-adherent	4	82
Adherent	12	1
VAS		
Non-adherent	7	4
Adherent	11	78

Table 3. Concordance of FM and VAS in Categorizing Non-adherence in Patients with IBD

	VAS	
Concordance (%)	**Non-adherent**	**Adherent**
FM	4	89
Non-adherent		
Adherent	5	1

Table 4. Percentages of Non-adherent Study Participants According to Age Categories and Employment Status

Characteristics	**VAS (% Non-adherent Patients)**		**MMAS-8 (% Non-adherent Patients)**		**FM (% Non-adherent Patients)**	
Young patients (<40 yr)	12.0	P = 0.63	26.9	P = 0.01	9.8	P = 0.03
Older patients (>40 yr)	10.2		13.7		4.8	
Age (≥per yr)	0.05	P = 0.27	0.33	P = 0.01	20.20	P = 0.01
Employed patients	12.7	P = 0.33	20.1	P = 0.30	8.1	P = 0.13
Unemployed patients	8.9		15.8		4.1	

DISCUSSION

In this large cross-sectional study, we compared the performance of 3 different tools for self-reported adherence assessment in patients with IBD. We found the MMAS-8, the VAS, and the FM to be significantly, yet moderately, correlated. Furthermore, all applied tools were able to identify young age and employment as risk factors for non-adherence to medical therapy.

Self-report is the most unobtrusive, cost-free, and accessible method to measure adherence.[17] The 8 questions in the MMAS-8 refer to several qualitative aspects of adherence behavior, whereas the VAS measures adherence on a single continuous scale and the FM is merely a categorization of the number of times patients forget taking their medication. Moderate discordances in adherence outcomes could be attributed to differences in scaling of these respective tools. For example, the impact of a "Yes" answer to one of the questions included in the MMAS-8 ("When you travel or leave home, do you sometimes forget to bring along your IBD-medication?") may differ for individual patients depending on the frequency and length of travels. In addition, a negative answer to the question "Did you take your medication yesterday?" in patients using methotrexate once weekly will result in an undervaluation of adherence of this particular patient. Moreover, the answer possibilities included in the FM may explain the moderate correlation with the other 2 tools because differences between adjacent answer categories are unequal. For example, the difference in adherence between "No, never" and "Very exceptional" is smaller compared with the difference between "1 to 3 times a week" and "more than 3 times a week."

Because no clinically accepted cutoff level for the FM is available, we defined non-adherence as a FM of "1 to 3 times a week" or more, based on the fact that forgetting medication only once weekly can be quantified as 85% adherent. This cutoff value may be somewhat arbitrary because there is quite a difference between forgetting medication only once (85% adherent) or 3 times weekly (58% adherent). Dichotomizing adherence outcomes may be useful for studies and provides easy to interpret data, but it can result in an unnatural categorization of human behavior.[18] This consideration should be taken into account when clinical consequences are based on categorized adherence outcomes.

A variety of factors are reported related to non-adherence in patients with IBD,[19–23] but only younger age and employment were found to be consistently associated with non-adherence in multiple studies.[5] All 3 applied tools were able to identify more young and employed patients as non-adherent, which proved to be statistically significant for younger age when using the MMAS-8.

To date, the VAS and FM for medication adherence have not been evaluated in IBD. The MMAS-8 has been validated in IBD against prescription claim information.[12] The results of this validation study could not be reproduced, however, because the MMAS-8 proved to be only predictive for adherence to thiopurine therapy in a more recent study.[24] For scientific purposes, the MMAS-8 has been widely applied throughout the medical field.[25–

28] Moreover, the use of the VAS and MMAS-8 have been jointly evaluated in hypertensive patients.[29] Both tools performed equally well in identifying non-adherent patients. In a systematic review on different methods for self-reported medication adherence, it was concluded that patients find it easier to estimate general adherence than to report a specific number of doses missed, and therefore, a VAS might be the easiest method from the perspective of patients.[18]

The advantage of using the MMAS-8 is that this tool may provide insight into barriers to adherence. However, due to disproportionate influences of answers to total adherence scores, this tool may fail to quantify and hence dichotomize adherence correctly. Also, this questionnaire may be too cumbersome and time-consuming for use in clinical practice. The VAS provides a quick impression of the adherence of patients and may most optimally reflect gradual variability of adherence. However, unintentional non-compliance cannot be measured with this tool, and patients may therefore overestimate their adherence.[30] The FM is straightforward as well, but its value is limited because adherence relies on more aspects than recall of medication only.[12] Based on these considerations, we feel that the VAS is the best choice when aiming to quantify adherence, whereas the MMAS-8 can be used additionally to identify qualitative barriers for non-adherence.

The strength of this study includes the large number of enrolled patients, comprising patients with CD and UC derived from both academic and nonacademic centers. However, our study might be subject to selection bias because patients who agree to participate can be expected to have a higher compliance to medication. A previously performed nonresponder analysis of the COIN study did not show any significant differences regarding patient and disease characteristics between responders and nonresponders, however.[9] Moreover, the primary aim of our study was to compare 3 methods for assessing medication adherence rather than an evaluation of adherence itself. Therefore, we believe that our findings can also be used in a population in which the average adherence is worse. The main limitation of this study is the lack of a gold standard for medication adherence. Self-assessment may result in an overestimation of adherence and has been found to be moderate-to-high concordant with other, more invasive measures of adherence.[31] Of note, even these more invasive measures of adherence have their own short-comings. For example, counting rates of prescription refills may not cover the actual drug use because patients may not actually take the dispensed medication.[5] Moreover, in therapeutic drug monitoring, adherence can be overestimated by a temporary improvement of compliance related to the approaching hospital appointment.[32,33]

In summary, in the absence of a gold standard, a simple and easy-to-use VAS seems the most appropriate tool for quantifying medication adherence in daily clinical practice. The MMAS-8 may be used additionally to provide insight in specific reasons for non-adherent behavior in patients with IBD.

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CHAPTER 4.2

Clinical predictors of future non-adherence in inflammatory bowel disease

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ABSTRACT

Background: Non-adherence to medical therapy is frequently encountered in patients with inflammatory bowel disease (IBD). We aimed to identify predictors for future (non)-adherence in IBD.

Methods: We conducted a multicenter prospective cohort study with adult patients with Crohn's disease (CD) and ulcerative colitis (UC). Data were collected by means of 3-monthly questionnaires on the course of disease and healthcare utilization. Medication adherence was assessed using a Visual Analogue Scale (VAS), ranging from 0-100%. Levels <80% were considered to indicate non-adherence. The Brief Illness Perception Questionnaire was used to identify illness perceptions. We employed a logistic regression analysis to identify patient- and disease- related factors predictive of non-adherence 3 months after the assessment of predictors.

Results: In total, 1,558 CD patients and 1,054 UC patients were included and followed for 2.5 years. On average, 12.1% of CD patients and 13.3% of UC patients using IBD-specific medication were non-adherent. Non-adherence was most frequently observed in patients using mesalazine (CD), budesonide (UC) and rectally administrated therapy (both CD and UC). A higher perceived treatment control and understanding of the disease were associated with adherence to medical therapy. Independent predictors of future non-adherence were age at diagnosis (OR 0.99 per year), non-adherence (OR 26.91), a current flare (OR 1.30) and feelings of anxiety/depression (OR 1.17), together with an area under the receiver-operating-characteristics curve of 0.74.

Conclusions: Lower age at diagnosis, flares, feelings of anxiety or depression, and non-adherence are associated with future non-adherence in patients with IBD. Altering illness perceptions could be an approach to improve adherence behavior.

INTRODUCTION

Non-adherence to medical therapy is frequently encountered in patients with inflammatory bowel diseases (IBD). Identification of patients at risk for non-adherence and a timely intervention aimed at improving adherence might prevent an unfavorable disease course associated with this behavior.[1,2] The mechanisms leading to non-adherence are presently incompletely understood. In previous studies, several socio-demographic factors such as younger age, gender, current employment and single status have been found to be associated with non-adherence.[3–7] However, the prognostic value of previously identified factors, based on multivariable prediction modeling, has not yet been assessed. Also, is unknown whether non-adherence at one time point predicts future non-adherence in the same individual.

According to the Common Sense Model[8], illness perceptions about IBD play a major role in the adjustment to this chronic illness, and may weaken the impact of clinical characteristics on clinical outcomes. However, the association between illness perceptions and adherence behavior has only been studied for anti-TNF users.[9]

The primary aim of this study was to identify easy-to-obtain clinical predictors for future non-adherence among IBD patients. Secondary, we aimed to identify illness perceptions that accompany non-adherent behavior.

MATERIAL AND METHODS

Patient population and study design

The COIN study (Costs of Inflammatory bowel disease in the Netherlands) is a large multicentre cohort study initiated in 2010 aimed at prospectively assessing the IBD-related healthcare costs, patient costs and productivity losses and Health-related Quality-of-Life (HrQoL).[10] All patients from seven university medical centres and seven general hospitals aged 18 years or older were eligible for participation, regardless of their current disease duration. The study design has previously been described in detail.[10]

Data collection

Patients were invited to fill out a web-based baseline questionnaire, followed by three-monthly questionnaires each with questions on HrQoL, disease activity scores, healthcare resources used, sick leave days, disease course items, medication used and medication adherence. Demographic and general characteristics (gender, age, age at diagnosis, IBD diagnosis) were included in the first questionnaire only.

Non-adherence to IBD-specific medication

Adherence to IBD-specific medication was self-assessed during each follow-up moment, and only applicable for this study if patients used IBD-specific medication. A Visual Analogue Scale ("VAS"), answering the question how well patients overall were taking their IBD medication on a scale ranging from 0% to 100% was used. 100% indicated a perfect adherence, 0% indicated very bad adherence. Medication adherence rates (VAS) <80% were considered non-adherent, rates ≥80% were considered adherent.[11,12] Distributions of medication adherence of study participants were presented with medians and interquartile ranges, and presented per person years. Adherence rates were presented per individual type of medication, per type of medication-administration (i.e. oral, parenteral, intramuscular and rectal), and per number of different types of IBD-medication per patient.

Outcome: future non-adherence

The main outcome: 'future' non-adherence was defined as being non-adherent in a three-months' time span following the assessment of candidate predictors. For example, a disease flare at T=6 months of follow-up was incorporated as a predictor for (non)-adherence at T=9 months of follow-up. Predictors at the first measurement in time were used to predict adherence at the second measurement in time, predictors at the second measurement

in time were used to predict adherence at the third measurement in time and so forth. Therefore, non-adherence was analyzed prospectively.

Candidate predictors

Based on previous studies[3–7,13] and clinical reasoning, we selected candidate predictors for future non-adherence that would be easy to obtain by a physician in the setting of the out-patient clinic.

Patient characteristics: gender, current employment, age at diagnosis, currently living apart vs. together in any form of relational partnership, smoking status (current, ex-smoker or never-smoker), high or low education level were assessed at baseline (high education meaning education beyond high school).

Disease related factors: type of IBD (CD or UC), disease duration, current self-reported flares, the short Crohn's disease Activity Index (CDAI)[14] for CD patients and the Modified Truelove and Witts Index (MTWSI)[15] for UC patients, and (peri)anal fistulas (for CD patients) were assessed at every 3-month time point.

Quality of life items: the separate five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) of the EQ-5D-3L instrument[16] were assessed at every 3-month time point for three functioning levels (no problems, some problems or severe problems). Answers were categorized into 'no problems' or 'any problems' (consisting of some problems or severe problems) regarding these five items. Health states were not analyzed in this study.

Sick leave due to IBD-related illness: patients were asked during follow-up whether they had been called in sick from both paid and unpaid (voluntary) work due to IBD-related illness during the past three months.

Non-adherence: Non-adherence was also included as a candidate predictor for non-adherent behavior after three months. This means that for example, an adherence measurement at T= 6 months of follow-up was incorporated as predictor of (non)-adherence three months later, at T=9 months of follow-up (and so forth).

Illness perceptions and adherence behavior

Once during follow-up (at 27 months after the start of the COIN study), the Brief Illness Perception Questionnaire (B-IPQ) was assessed.[17,18] This nine-item questionnaire explores the cognitive and emotional representation of illness. The cognitive representation consists of identity, consequences, causes, timeline and cure or control. The emotional representation incorporates negative reactions such as fear, anger and distress. Items were assessed on a 10-point Likert scale, for example "How much does your illness affect your life?" 0 ("not at all") – 10 ("severely affects my life"). Mean scores were compared between adherent and non-adherent patients, and logistic regression analysis was performed to study the association between individual items and non-adherence at the same moment.

Statistical analysis

We used logistic regression analysis to estimate the association between the candidate predictors (measured at each time point) and the adherence outcome measured three months later. A residual (i.e. generalized estimating equation type) covariance matrix was included in the analyses to correct for repeated measurements within patients.[19] Time was included by allowing disease duration to increase with the follow-up. We evaluated all candidate predictors in a multivariable ('full') model regardless of univariable statistical significance. Independent predictors were subsequently selected using backwards selection. Type of IBD, gender and age at diagnosis were always retained in the final selection, regardless of statistical significance. The final selection was based on Akaike's Information Criterion, which corresponds to a p-value of 0.157 for a predictor with a single degree of freedom (i.e. one regression coefficient in the model). This criterion was chosen, as the 'standard' p-value for statistical significance of 0.05 may be too stringent for the evaluation of predictors.[20] The model's ability to discriminate between adherent and non-adherent patients was estimated with the c-statistic, which is similar to the area under the receiver-operating-characteristic (ROC) curve for dichotomous outcomes at a single time point. This measure was not corrected for repeated measures to obtain a discriminative ability that fully incorporates differences in non-adherence both within and between patients at different time-points (hence it will be reported without potentially biased confidence intervals). Additionally, the model was calibrated to evaluate its performance in both CD patients and UC patients separately (see appendix for details). To retain full statistical power, we used multiple imputation techniques to account for missing data.[21] Data were imputed five times; all statistical analyses were subsequently performed on the five imputations separately. Missing values were imputed by a combination of health status variables (treatment variables, disease activity, psychological measurements (disease-related HrQoL and general HrQoL) including the outcomes and all predictors (full details available on request). The results of the analyses were pooled using Rubin's rule.[22] The analyses of the association between illness perceptions and medication adherence were cross-sectional performed, since this questionnaire was only assessed once. Medication use was reported per person-years (i.e. the total number of medication prescriptions divided by time; time meaning the multiplication of the number of patients with the number of three monthly time period in which the medication was used). Answers to the Brief Illness Perceptions Questionnaire were not imputed. Multiple imputation techniques and the analyses of adherence distributions were performed with SPSS version 21.0 (Armonk, NY: IBM Corp); prediction modeling was performed with SAS version 9.2, Cary, NC.

Ethical considerations

This study was carried out with the approval of the Medical Ethics Committee (MEC) of the University Medical Center Utrecht.

RESULTS

Patient population

In total, 2,612 patients (1,588 CD and 1,054 UC) participated in this study (Table 1). Patients were followed for a maximum of 2.5 years. The response rate after two years was 47% for CD and 54% for UC patients.[23] An overview of total responders and missings per time-point is shown in appendix 1. A non-responder analysis revealed that responders were older and had a longer disease duration as compared with non-responders (patients who were lost to follow-up). Adherence scores of the responding study population after 2.5 years were not different compared with the total study population at the start of the study. Mean adherence scores at the first time point were higher in patients who remained in study throughout the full follow-up period (responders) compared to patients who were lost to follow-up (mean VAS 93.0 (SD 12.0) versus 90.1 (SD 16.0), $p<0.01$). After multiple imputation, no missing data remained.

Distribution of medication adherence

At three months of follow-up after inclusion, 75.9% of patients used medication for IBD. Reported median adherence scores were high at three months, and did not differ between CD and UC patients (VAS 95.4% (IQR 88.3 - 100) for CD patients and 95.2% (IQR 87.5 – 100) for UC patients (Table 1).
In CD patients, non-adherence was most frequently observed in patients using mesalazine (Table 2), in patients using rectally administrated medications, in patients with three administrations of medication per day, and in patients on monotherapy as compared with patients using two or three different kinds of IBD-medication. In UC patients, non-adherence was most frequently seen in patients using budesonide, rectally administrated medication, in patients with five or more administrations of medication per day, or in patients on monotherapy (Table 3).

Medication adherence during follow-up

During each cycle of follow-up, the majority of adherent CD and UC patients remained adherent within the three subsequent months after each measurement (91.1% and 92.2%, respectively). Of patients who were non-adherent at a single time point, the majority of CD and UC patients switched to adherent behavior within the three subsequent months (61.5% and 61.1%, respectively) (Fig. 1).

Table 1. Patient characteristics*

Characteristics	CD patients (n=1,558)	UC patients (n=1,054)
Demographic characteristics at baseline		
Male gender, n (%)	574 (36.8)	527 (50.0)
Age – years, mean (SD)	46.9 (13.7)	49.2 (13.3)
Low education, n (%)	1008 (64.7)	614 (58.3)
Currently employed, n (%)	738 (47.4)	614 (58.3)
Smoking, n (%)		
Current	329 (21.1)	95 (9.0)
Never	781 (50.1)	603 (57.1)
Ex-smoker	448 (28.8)	358 (33.9)
Disease characteristics at baseline		
Disease duration , median (IQR)	15.3 (7.9 – 25.8)	12.8 (6.2 – 20.9)
Disease localization, n (%)		
Colon	431 (27.7)	1014 (96.2)
Small intestine	306 (19.6)	0 (0.0)
Both colon and small intestine	768 (49.3)	0 (0.0)
Unknown	53 (3.4)	40 (3.8)
Disease in remission, n (%)	1329 (85.4)	881 (83.6)
Stoma, n (%)	192 (12.3)	61 (5.8)
Pouch, n (%)	28 (1.8)	94 (8.9)
Fistula, n (%)	220 (14.1)	0.0 (0%)
Abdominal surgery in the past, n (%)	843 (54.1)	194 (18.4)
Medication use at three months of follow-up, n (%)		
5-ASA	307 (23.5)	596 (65.2)
Steroids	134 (10.2)	70 (7.6)
Immunosuppressive drugs (Aza/6MP/MTX)	463 (35.4)	203 (22.2)
Anti-TNF	299 (22.9)	35 (3.8)
None	337 (25.8)	198 (21.7)
Medication adherence at three months of follow-up, n (%)		
VAS score, median (IQR)	95.4 (88.3 – 100)	95.2 (87.5 – 100)
Non-adherent n (%)	189 (12.1)	140 (13.3)
Adherent n (%)	1,369 (87.9)	914 (86.7)

**In this table, multiple imputation techniques were only applied to medication adherence. Abbreviations used: CD: Crohn's disease, UC: ulcerative colitis, SD: standard deviation; IQR: interquartile range: ASA: aminosalicylic acid; Aza: azathioprine; 6MP: 6-mercaptopurine; MTX: methotrexate; TNF: tumour necrosis factor; VAS: Visual Analogue Scale; IQR: interquartile range*

Prediction of future non-adherence

Lower age at diagnosis, a current flare, self-reported anxious or depressed feelings (EQ-5D-3L) and current non-adherence were independent predictors for future non-adherence in IBD (unadjusted associations: Table 5; final prediction model: Table 6). Among these factors, non-adherence was the highest contributing predictor with an adjusted odds ratio of 26.91 (95% CI 22.67-31.94). The ROC area of the final model was 0.74. Calibration slopes for CD and UC patients showed values of 0.96 (95% CI 0.89 – 1.03) and 1.05(95% CI 0.96-1.14), respectively (see appendix 2 for details).

Illness perceptions

In CD patients, a better control over the disease and a higher level of perceived help of treatment was associated with a lower risk of non-adherent behavior (Table 4). In UC patients, longer perceived disease duration (indicating that patients think their illness will continue longer), a better control over the disease, a higher level of understanding of the disease and a higher influence of the disease on the mood of patients was associated with a lower risk for non-adherent behavior.

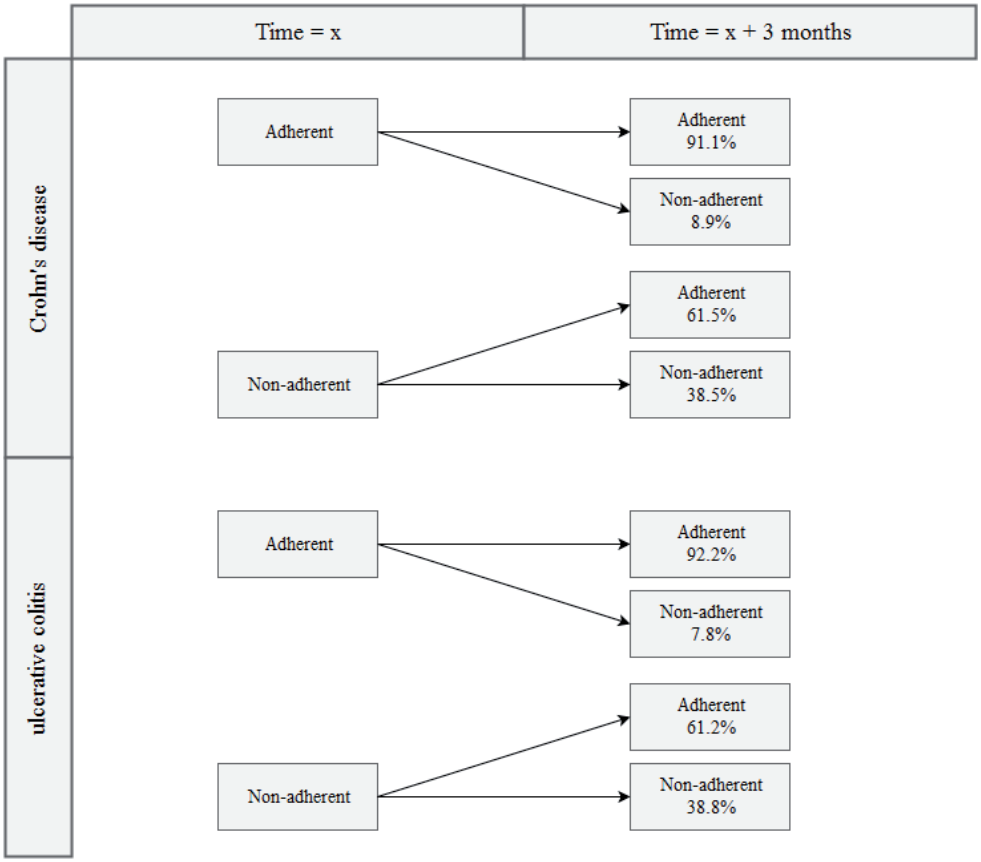

Fig.1: Development of medication adherence during follow-up

In this figure, all adherence measurements of individual patients during 2.5 years of follow-up have been encountered. The percentages represent the average successive development of adherence per cycle of three months.

Table 2. Medication use and non- adherence in CD patients, per person years

	Adherent n/n person years (%)	**Non-adherent n/n person years (%)**
Type of medication		
Mesalazine	5688/7100 (80.1)	1412/7100 (19.9)
Sulfalazine	303/372 (81.5)	69/372 (18.5)
6-Mercaptoprine	1839/2203 (83.5)	364/2203 (16.5)
Budesonide	1607/1912 (84.1)	305/1912 (15.9)
Prednisone (tablets)	658/772 (85.2)	114/772 (14.8)
Azathioprine	6988/8156(85.7)	1168/8156 (14.3)
Methotrexate	907/1056 (85.9)	150/1056 (14.1)
Infliximab	3031/3476 (87.2)	445/3476 (12.8)
Prednisone (withdrawal schedule)	506/572 (88.4)	67/572 (11.6)
Adalimumab	3709/4172 (88.9)	463/4172 (11.1)
Type of medication administration		
Rectal	76/112 (67.9)	36/112 (32.1)
Oral	15122/18237 (82.9)	3114/18237 (17.1)
Intramuscular	4422/5024 (88.0)	602/5024(12.0)
Parenteral	3067/3524 (87.0)	457/3524(13.0)
Number of pills per day in patients with orally administrated medication		
One	4730/5541 (85.4)	810 /5541 (14.6)
Two	1698/2050 (82.8)	352/2050 (17.2)
Three	1554/1954 (79.5)	400/1954 (20.5)
Four	539/672 (80.2)	133/672 (19.8)
Five and more	358/440 (81.5)	82/440 (18.5)
Number of different types of medication per patient		
One (monotherapy)	12970/15703 (82.6)	2734/15703 (17.4)
Two	5086/5848 (87.0)	762/5848 (13.0)
Three	606/696 (87.0)	90/696 (13.0)

Table 3. Medication use and non- adherence in UC patients, per person years

	Adherent n/n person years (%)	**Non-adherent n/n person years (%)**
Type of medication		
Mesalazine	13084/15488 (84.5)	2404/15488(15.5)
Sulfalazine	166/184 (90.4)	18/184 (9.6)
6-Mercaptoprine	1382/1529 (90.1)	151/1529 (9.9)
Budesonide	454/576 (78.8)	122/576 (21.3)
Prednisone (tablets)	418/464 (90.2)	46/464 (9.8)
Azathioprine	3178/3691 (86.1)	513/3691 (13.9)
Methotrexate	181/224 (80.7)	43/224 (19.3)
Infliximab	810/919 (88.2)	109/919 (11.8)
Prednisone (withdrawal schedule)	397/440 (90.2)	43/440 (9.8)
Adalimumab	248/280 (88.6)	32/280 (11.4)
Type of medication administration		
Rectal	438/520 (84.2)	82/520 (15.8)
Oral	14870/17482 (85.1)	2612/17482 (14.9)
Intramuscular	421/496 (84.8)	75/496 (15.2)
Parenteral	865/975 (88.7)	110/975 (11.3)
Number of pills per day in patients with orally administrated medication		
One	3012/3594 (84.8)	582/3594 (16.2)
Two	3042/3506 (86.8)	464/3506 (13.2)
Three	2157/2466 (87.5)	309/2466 (12.5)
Four	790/892 (88.5)	102/892 (11.5)
Five and more	442/552 (80.0)	110/552 (20.0)
Number of different types of medication per patient		
One (monotherapy)	6758/8717 (84.6)	1959/8717 (15.4)
Two	3741/4319 (86.6)	578/4319 (13.4)
Three	652/748 (87.2)	96/748 (12.8)

Table 4. Association of Illness perceptions with non-adherence in IBD patients*

Illness perception item, mean (SD)	Adherent	Non-adherent	OR for non-adherence	95% CI	p-value
CD patients, n=259					
Influence of disease on your life	4.7 (2.8)	4.9 (2.4)	1.03	0.90 – 1.19	0.70
Thoughts on disease duration	9.9 (0.6)	9.8 (1.2)	0.76	0.02 – 33.24	0.89
Control over disease	5.6 (2.7)	4.7 (2.7)	0.89	0.78 – 1.02	0.08
Level of help of treatments	7.4 (2.2)	6.2 (2.7)	0.83	0.70 – 0.98	0.03
Level of disease complaints	4.4 (2.7)	4.6 (2.2)	1.03	0.88 – 1.22	0.68
Level of concern regarding disease	3.8 (2.6)	3.7 (2.1)	0.99	0.85 – 1.15	0.88
Level of disease understanding	7.1 (2.4)	6.5 (2.7)	0.91	0.78 – 1.06	0.22
Influence of disease on mood	3.5 (2.6)	4.0 (2.6)	1.06	0.92 – 1.24	0.42
UC patients, n=185					
Influence of disease on your life	3.2 (2.5)	3.4 (2.3)	1.03	0.85 – 1.25	0.74
Thoughts on disease duration	9.8 (0.9)	9.1 (2.0)	0.72	0.54 – 0.97	0.03
Control over disease	6.2 (2.9)	4.9 (303)	0.88	0.75 – 1.03	0.10
Level of help of treatments	7.7 (2.4)	7.1 (2.3)	0.90	0.75 – 1.09	0.28
Level of disease complaints	3.1 (2.3)	3.7 (2.2)	1.12	0.89 – 1.42	0.32
Level of concern regarding disease	2.9 (2.4)	3.6 (2.1)	1.14	0.92 – 1.40	0.22
Level of disease understanding	7.4 (2.4)	6.0 (2.8)	0.82	0.68 – 0.98	0.03
Influence of disease on mood	2.4 (2.3)	3.6 (2.8)	1.21	0.99 – 1.48	0.06

** In this table, multiple imputation techniques were not applied to illness perceptions. Illness perceptions were assessed once at t=27months of follow-up. Abbreviations used: SD: standard deviation; OR: Odds Ratio, CI: Confidence interval, IQR: interquartile range*

Table 5. Unadjusted association between each candidate predictor and *subsequent* (non) adherence (after three months of follow-up) in IBD patients

Potential predictors	OR	95% CI	p-value
Patient factors			
Male gender (vs female gender)	0.92	0.77 – 1.10	0.37
Current employment (vs unemployment)	1.16	0.92 – 1.48	0.27
Higher age at diagnosis, per year	0.99	0.98 – 0.99	<0.01
Living alone (vs living together)	0.96	0.64 – 1.42	0.84
Married (vs unmarried)	1.10	0.81 – 1.49	0.58
Low education (vs high education)	1.11	0.93 – 1.33	0.25
Smoking status			
Current	1.44	1.11 – 1.87	0.01
Ex-smoker	1.09	0.89 – 1.33	0.40
Never-smoker*	-	-	-
Health and disease related factors			
CD (vs UC diagnosis)	1.13	0.94 – 1.35	0.21
Disease duration, per year	1.00	0.99 – 1.01	0.53
Flare (vs remission)	1.26	1.08 – 1.47	<0.01
CDAI score (CD patients)	1.00	1.00 – 1.00	0.78
MTWSI score (UC patients)	1.02	0.97 – 1.08	0.50
(Peri-anal)fistula (CD patients)	1.15	0.82 – 1.61	0.45
EQ-5D domains			
Mobility (any problems vs. no problems)	1.11	0.91 – 1.36	0.38
Self-care (any problems vs. no problems)	1.06	0.72 – 1.57	0.82
Usual activities (any problems vs. no problems)	1.05	0.90 – 1.22	0.64
Pain/discomfort (any problems vs. no problems)	1.19	1.03 – 1.37	0.03
Anxiety/depression (any problems vs. no problems)	1.31	1.12 – 1.54	<0.01
Sick leave due to IBD-related illness	1.07	0.85 – 1.34	0.60
Non-adherence #	14.09	9.56 – 16.41	<0.01

Abbreviations used: OR: Odds ratio, CI: confidence interval, OR: Odds ratio, CI: confidence interval, CDAI: Crohn's disease activity index, MTWSI: modified Truelove and Witts severity index, VAS: visual analogue scale

Notes:

** reference category*

#Non-adherence three months before the outcome

Table 6. Independent predictors for future non-adherence in IBD patients

Independent predictors	Adjusted OR	95% CI	p-value
Male gender (vs female gender)	1.05	0.89 – 1.24	0.57
Current employment (vs unemployment)	1.01	0.86 – 1.19	0.88
Higher age at diagnosis, per year	0.99	0.99 – 1.00	0.01
Flare (vs remission)	1.30	1.08 – 1.57	0.01
Anxiety/depression* (any problems vs. no problems)	1.17	0.97 – 1.40	0.11
Non-adherence#	26.91	22.67 – 31.94	<0.01

Abbreviations used: OR: Odds ratio, CI: confidence interval, OR: Odds ratio, CI: confidence interval, CD: Crohn's disease, UC: ulcerative colitis,

Notes:

#Non-adherence three months before the outcome.

** As measured via the EQ-5D domain – anxiety/depression*

Area under the curve (C-statistic) of final prediction model: 0.74.

DISCUSSION

In this large prospective cohort-study, we identified lower age at diagnosis, current flares, self-reported anxious or depressed feelings and current non-adherence as independent predictors for future non-adherence to medical therapy in IBD. Our final prediction model for future non-adherence performed reasonably well for the total IBD population, and for the CD or UC group separately.[24] Adherence to medical therapy was found to be associated with higher perceived treatment control and comprehension of the disease.

Our results confirm that lower age is a predictor of non-adherence.[3,25] Gender was not found to predict non-adherence. Both female and male gender have been identified as a predictor of non-adherence in previous studies.[7,26–30] These studies showed a wide range in study design, study population and methods to define non-adherence, which complicates pooling of the results. In the only study which included (self-reported) depression and anxiety as candidate predictor for non-adherence, an association was observed between these factors and non-adherence.[31] In addition, we identified active disease as a predictor for subsequent non-adherent behavior. This might imply that active disease precedes non-adherence in time. However, it is conceivable that active disease merely results from non-adherence, and that non-adherent behavior is sustained longer in time, regardless of the emerge of active disease in some patients.

Accordingly, current non-adherence was found to be the best independent predictor for future non-adherence with an adjusted OR of 26.91. This infers that non-adherence may be consistent over longer periods of time (i.e. longer than 3 months) in some patients, thus negatively affecting the disease course. However, we also observed that a considerable number of non-adherent patients reported to become adherent after a follow-up of three months. Based on these results, we can conclude that adherence behavior in IBD patient shows variability over time, at least in our cohort. Therefore, adherence behavior may be amendable (Fig. 1).

Non-adherence was most frequently observed in patients using rectally administrated medicine, patients on monotherapy and in patients having multiple administrations per day. It can be speculated that patients on monotherapy have quiescent disease and that multiple administrations per day complicate full adherence. However, it may also be an indication that the VAS applies more easily to monotherapy. Also, a higher perceived treatment control and understanding of disease was associated with adherence to medical therapy. Higher adherence has previously been found to be associated with stronger perceptions of necessity of treatment and with fewer concerns about (negative aspects of) treatment among patients with long-term conditions.[33] Also, a feeling of adequate information about the disease, medication and illness beliefs and the absence of psychological distress have been found to be associated with adherence behavior in IBD patients.[6,9] Our findings corroborate the Common Sense Model, in which it is stated that patients' beliefs play an important role in the modification to the disease.[8,34] Because these consistent findings

open new avenues for therapeutic interventions, we recommend to discuss perceptions about the disease and related treatment with all IBD patients, especially if non-adherence is suspected. Of note, the B-IPQ has only nine questions. Thus, illness perceptions, including possible barriers for non-adherence, can easily be obtained.

Strengths of this study include the longitudinal nature of the study, resulting in repetitive assessments of medication adherence among IBD patients. This design enabled us, for the first time, to predict future (non)-adherence in individual patients and to report on changes in adherence behavior over time. Moreover, this allowed for extensive correction for confounding. Some aspects of our findings warrant comment. First of all, self-report as a method to assess adherence can be regarded a limitation. Patients may over- or underestimate their adherence. Non-adherence identification can either be based on biological assays[32], pharmacy refill data[1] or questionnaires.[3] In general, questionnaires tend to have a moderate-to-high concordance with other (more invasive) measures of medication adherence.[35] Self-report is an easy and accessible method to assess medication adherence.[12] Using self-reported VAS, non-adherence was observed in 12.1% of CD patients and 13.3% in UC patients. Previous studies report non-adherences rates ranging from 7% to 72%, with majority of studies reporting 30% to 45% of patients to be non-adherent.[5] Variability of measurement techniques and patient populations presumable explain the significant heterogeneity among studies. Since self-report is less objective compared with more invasive methods, the number of true non-adherent patients in our cohort is conceivably larger. Moreover, since patients in our cohort have a median IBD disease duration of more than 10 years, our cohort may represent a group of patients with improved adherence behavior compared with cohorts including predominantly newly diagnosed IBD patients. We have previously compared the performance of the employed VAS to measure adherence with the validated Modified Morisky Adherence Scale (MMAS-8) [36–38], and found this tool to be highly accurate for assessing adherence in IBD patients. [12] The VAS may best be used for oral medications. Regarding biologicals, its use might be limited since adherence rates for weekly or monthly administrations might be less accurate. Of note, a VAS is a crude method for quantifying adherence but fails to specify which (number of) pills or other medication is not consumed and for what reason. Second, cohort studies may be prone to selection bias, since patients who agree to participate might be more adherent to medical therapy. However, a previously performed non-responder study of our cohort did not show any significant differences regarding patient- and disease characteristics between responders and non-responders.[10] Third, during follow-up of cohort studies, the amount of missing data among variables generally increases over time. In the COIN study, many patients were lost to follow up over time. A comparison between patients who completed the two year follow-up questionnaire with those who were lost to follow-up in our study revealed that long-term responders were older and had longer disease duration.[23] Although the percentage of non-adherence among patients did not differ between the first and last assessment, selection bias could not be fully excluded.

Mean adherence scores at the first time point were higher in patients who remained in the study throughout the full follow-up period compared to patients who were lost to follow-up. In order to minimize possible (selection) bias, all analyses were carried out after performing multiple imputation techniques.[22] Despite these limitations, we feel confident that our study reliably reflects long-term adherence behavior amongst IBD patients and provides consistent predictive factors during the course of disease.

In conclusion, physicians should be aware that patients younger at diagnosis, patients with a disease flare, with self-reported anxious/depressed feelings, and patient who are currently non-adherent tend to be future non-adherent. Timely identification of IBD patients at risk for non-adherence and interventions aimed at illness perceptions might improve adherence and prevent a disadvantageous course of disease in the long run.

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Appendix 1: Number of responders of the COIN cohort per time point

Time point	Number of responders	Missings
Baseline	3030	0
3 months	2557	473
6 months	1790	1240
9 months	1710	1320
12 months	1871	1159
15 months	1745	1285
18 months	1672	1358
21 months	1487	1543
24 months	657	2373
27 months	934	2096

Appendix 2: Calibration of our prediction model

Methods: For the utility of a prediction model, it is important that the predicted probability of a model is the same as the observed probability. This can be evaluated only in individual patient data, as an individual patient at a single time-point only has or does not have the outcome (non-adherence in this case) of interest.

The calibration can be calculated by estimating for each patient the summation of their individual values on the predictor weighted (multiplied) by the regression coefficients from the prediction models. This yields the linear predictor, which corresponds with a predicted probability. This value can be used in a regression analysis similar to the model (e.g. logistic regression) as the only predictor. The constant of the model and the regression coefficient (beta) of the aforementioned linear predictor combined may be interpreted as the calibration of the model. Under perfect calibration, their respective values will be 0 (the constant) and 1 (the beta for the linear predictor). See Steyerberg (2001) for details.[1]

In general, the most rigorous way to evaluate calibration is in a new dataset with predictor information and outcomes in patients for whom the prediction model may be used. Here, we used calibration techniques to evaluate if the model is sufficiently calibrated in the two groups of patients, CD and UC patients, included in the study, by estimating the constant and beta for each disease separately. Significant deviations from the ideal values of 0 and 1 may be taken as miscalibration.

Results: Calibration slopes for CD and UC patients showed values of 0.96 (95% CI 0.89 – 1.03) and 1.05(95% CI 0.96-1.14), with constants of -0.05 (95% CI -0.20-0.09) and 0.08 (95% CI -0.10-0.26) respectively, slightly deviating from 1 (for the slope) and 0 (for the constant) for both groups combined

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CHAPTER 4.3

Medication non-adherence and its consequences for costs, flares and quality-of-life among inflammatory bowel disease patients: a prospective cohort study

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Submitted

ABSTRACT

Background: Consequences of non-adherence to medical therapy in inflammatory bowel diseases (IBD) are largely unknown. We aimed to investigate the impact of non-adherence on the disease course, healthcare costs and the Health-related Quality-of-Life (HrQoL) among adult patients with IBD.

Methods: Patients with Crohn's disease (CD) and ulcerative colitis (UC) were prospectively followed for 2.5 years. Data were collected on flares, IBD-specific healthcare utilization, HrQoL and medication adherence, using three-monthly questionnaires. Healthcare costs were calculated by multiplying healthcare consumption with corresponding unit prices and expressed in 2015 Euros. Adherence was assessed by a visual analogue scale (VAS), ranging from 0 to 100%; and were categorized into low- (<50%), moderate- (50-<80%) and high (≥80%). We used a generalized linear mixed model, incorporating a correction for time-dependent measurements, to study the longitudinal impact of adherence on costs, flares and HrQoL.

Results: In total, 1,558 CD and 1,054 UC patients were evaluated, of whom 75.9% used IBD-related medication. Three percent was low adherent, 13% was moderate adherent, and 84% was high adherent. Low adherence was associated with an increase in healthcare costs after 6 months of follow-up in CD patients (+€255 (+42%)p=0.03). Low adherence was not statistically significantly associated with the development of flares or a decrease in HrQoL.

Conclusions: Low adherence is associated with higher healthcare costs during follow-up in CD patients. Improving adherence might therefore result in a reduction of healthcare costs.

INTRODUCTION

Non-adherence to medical therapy is frequently encountered in patients with inflammatory bowel diseases (IBD). Several studies have focused on identifying non-adherence[1–5] and on interventions to improve adherence.[6–8]

Previous studies found that non-adherence to mesalazine therapy was associated with a higher risk for relapse in ulcerative colitis (UC) patients[9,10] and IBD patients in general.[11] The impact of nonadherence on disease specific quality-of-life has not been widely studied, however, and the economic impact of non-adherence remains largely unknown. Presently, the economic consequences of non-adherence have solely been studied in UC patients using 5-ASA compounds, and in Crohn's disease (CD) patients on infliximab. In these patients, non-adherence was associated with higher healthcare costs.[12– 16]

Our aims were to explore the impact of medication adherence on the disease course, healthcare utilization, healthcare costs and Health-related Quality of Life (HrQoL) in adult patients with CD or UC, using a prospective cohort study design.

METHODS

Patient population and study design

Data from the COIN study (Costs of Inflammatory bowel disease in the Netherlands) were used for this study. The COIN study is a large multicentre cohort study initiated in 2010, aimed to prospectively assess the IBD-related costs and HrQoL.[17] All IBD patients from seven university medical centres and seven general hospitals aged 18 years or older were eligible for participation. Patients were invited by letter to participate. Respondents formed the COIN cohort. The study design has been described previously in detail.[17]

Data collection

Patients filled-out a web-based baseline questionnaire, followed by three-monthly questionnaires. At baseline, demographic data (i.e. gender, age, education, employment and smoking status), disease course items (i.e. disease duration, disease localisation, current flare, stoma, pouch, fistula and previous abdominal surgeries), HrQoL and disease activity scores were collected. Used healthcare resources, disease items, HrQoL, disease activity scores and medication adherence scores were collected during at every three moths-time point during the study.

Medication adherence assessment

Adherence to IBD-specific medication was self-assessed at each follow-up moment. We used a visual analogue scale ("VAS", ranging from 0% to 100%), answering the single question how well patients were taking their daily IBD-medication, with 100% indicating a perfect adherence. Medication adherence rates (VAS) ≥80% were considered adherent,[18] rates of 50 - 80 were considered moderate adherent and rates ≤50 were considered low adherent. Adherence scores were only applicable for this study if patients used IBD-specific medication.

Outcome variables and covariables

Healthcare utilization

Units of IBD-specific healthcare utilization were self-reported and collected every three months. Resource utilization of healthcare was categorized under the following categories: (1) IBD-related outpatient clinic visits, including the number of outpatient physician consultations (i.e. gastroenterologist, internist, surgeon and rheumatologist), visits to IBD- or stoma-nurses and dieticians, and IBD-related visits to the general practitioner; (2) IBD-

related diagnostic procedures including number and type of gastrointestinal endoscopies, radiological procedures and blood tests; (3) medication use, including all IBD-specific drugs; (4) IBD-related hospitalization, defined as the number of days hospitalized, including number of days at the intensive care unit; and (5) IBD-related (abdominal) surgeries.

Healthcare costs

Healthcare costs were obtained by multiplying units of self-reported healthcare utilization by their corresponding unit prices per three months of follow-up.[17,19,20] Costs were expressed in Euros for the years 2015. Total healthcare costs were subdivided into medication costs and 'other healthcare costs', including costs for hospitalizations, diagnostic procedures, surgeries and outpatient clinic visits (hereafter referred to as 'other healthcare costs'). Of note, the 2015 exchange rate between Euros and US Dollars was 0.902, and 0.805 when applying a purchasing power parity [PPP] approach.[21]

Disease severity

Disease severity was defined by both the presence of self-reported flares ("do you currently suffer from a flare of disease?") and the level of disease activity. For CD and UC, the shortened Crohn's Disease Activity Index (Short CDAI) and the modified Truelove Witts Severity Index (MTWSI) were employed, respectively.[22,23]

Health-related quality-of-life

We used the Dutch version of the IBD-Questionnaire (IBDQ) to assess disease specific HrQoL, which consisted of four domains, i.e. bowel-, systemic-, social-, and emotional symptoms. [24] Generic HrQoL was measured by employing the EuroQol EQ-5D-3L instrument, which consists of a descriptive system based on five dimensions: mobility, self-care, usual activities, pain and depression/anxiety, with three levels of functioning (no-, any-, or severe problems). [25,26] Health states were scored using the Dutch tariff to obtain EQ-5D-3L summary indices (EQ5D-index scores) ranging from 0 (representing death) to 1 (representing full health), and negative values indicating health states worse than death.

Statistical analysis

Distributions of medication adherence of study participants were presented with medians and interquartile ranges. We analysed the impact of low, medium and high adherence on total three-monthly healthcare costs, other healthcare costs, flares, and HrQoL three and six months following the assessment of adherence in CD and UC patients separately. We used a generalized linear mixed model for the continuous outcomes (costs, IBDQ, EQ5D-index) and dichotomous outcome (flares) to correct for timedependent measurements. Cost data were not normally distributed and therefore log-transformed. Due to log-transformation, patients with no healthcare costs were not included in cost analyses. All outcomes were adjusted for age at diagnosis, disease duration, smoking, gender and previous disease activity scores. We incorporated a random intercept and a random effect for disease duration (increasing during follow-up) in each of the analyses. For dichotomous outcomes such as flares, a random effect for disease duration was not estimable. Therefore we estimated these models with a random intercept only. The validity of the model of continuous outcomes (i.e. distributional assumptions and homoscedasticity) was assessed with residual plots. Since the results of the analysis of costs is not straightforward (due to the log transformation), we presented all results as estimated mean costs, transformed back to Euros, for low, medium and high adherence. To account for missing data during follow-up, we used multiple imputation techniques.[27] Data (i.e. adherence scores, IBDQ, EQ5D- index scores and disease activity scores) were imputed five times. All statistical analyses were subsequently performed on the five imputations separately. The results of the analyses were pooled using Rubin's rule.[28] P-values <0.05 were considered statistically significant. Multiple imputation techniques were performed with SPSS version 21.0 (IBM corp, Armonk, NY). All other analyses were performed with SAS version 9.4, Carry, NC.

RESULTS

Patient population

In total, 2,612 patients (1,558 CD and 1,054 UC) participated in this study (Table 1). Patients were followed for a maximum of 2.5 years. The response rate after two years was 47% for CD and 54% for UC patients.[29] A non-responder analysis has been published previously. [29] Responders were older ($p<0.01$) and had longer disease duration ($p<0.01$) than non-responders. After multiple imputation, no missing data regarding the outcomes remained. At inclusion, CD and UC patients were on average 47 (Standard deviation (SD) 14) and 49 (SD 13) years old, and 85.4% and 83.6% of patients were in remission at baseline (Table 1).

Medication adherence

At three months of follow-up, 75.9% of patients used medication for IBD. Reported median adherence scores were high at three months, and did not differ between CD and UC patients (VAS 95.4% (IQR 88.3 - 100) for CD patients and 95.2% (IQR 87.5 – 100) for UC patients (Table 1)). Using the predefined cut-off values, 85% of CD patients and 84% of UC patients were categorized as adherent. Adherence rates during follow-up, and differences in adherence scores between different types of IBD medication have been previously reported.[30] In short, non-adherence (VAS score <80%) was most frequently observed in patients using mesalazine (CD), budesonide (UC) and rectally administrated compounds (in both CD and UC). Moreover, the majority of adherent CD and UC patients remained adherent within the three subsequent months after each measurement (91.1% and 92.2%, respectively). Of patients who were nonadherent at a single time point, the majority of CD and UC patients switched to adherent behaviour within the three subsequent months (61.5% and 61.1%, respectively).

Healthcare costs associated with low adherence

In CD patients, low adherence was associated with an increase in total three-monthly healthcare costs (+ 42% relative to high adherent patients (mean €868 vs. €613), $p=0.03$) and other three-monthly healthcare costs (+116% (mean €454 vs. €211), $p<0.01$) after six months of follow-up (Fig.1, Supplementary Table 1). Specifying the components of these 'other healthcare costs,' hospitalization costs were found to be higher for low adherent patients than for high adherent patients (€542 vs. €193) (Supplementary Table 2).
In UC, total, medication and other healthcare costs were higher for low adherent patients, which did not reach statistical significance (Fig.1, Supplementary Table 1).
Of note, on average 11.5% of IBD patients had zero euro total healthcare costs per three months.

Table 1. Patient characteristics

Characteristics	CD patients (n=1,558)	UC patients (n=1,054)
Demographic characteristics at baseline		
Male gender, n (%)	574 (36.8)	527 (50.0)
Age – years, mean (SD)	46.9 (13.7)	49.2 (13.3)
Low education, n (%)	1008 (64.7)	614 (58.3)
Currently employed, n (%)	738 (47.4)	614 (58.3)
Smoking, n (%)		
Current	329 (21.1)	95 (9.0)
Never	781 (50.1)	603 (57.1)
Ex-smoker	448 (28.8)	358 (33.9)
Disease characteristics at baseline		
Disease duration , median (IQR)	15.3 (7.9 – 25.8)	12.8 (6.2 – 20.9)
Disease localization, n (%)		
Colon	431 (27.7)	1014 (96.2)
Small intestine	306 (19.6)	0 (0.0)
Both colon and small intestine	768 (49.3)	0 (0.0)
Unknown	53 (3.4)	40 (3.8)
Disease in remission, n (%)	1329 (85.4)	881 (83.6)
Stoma, n (%)	192 (12.3)	61 (5.8)
Pouch, n (%)	28 (1.8)	94 (8.9)
Fistula, n (%)	220 (14.1)	0.0 (0%)
Abdominal surgery in the past, n (%)	843 (54.1)	194 (18.4)
Medication use at three months of follow-up, n (%)		
5-ASA	307 (23.5)	596 (65.2)
Steroids	134 (10.2)	70 (7.6)
Immunosuppressive drugs (Aza/6MP/MTX)	463 (35.4)	203 (22.2)
Anti-TNF	299 (22.9)	35 (3.8)
None	337 (25.8)	198 (21.7)
Total three-monthly healthcare costs at three months of follow-up, mean (95% CI), 2015 Euro		
Healthcare costs	€1,739 (€1,579 - €1,899)	€637 (€540 - €733)
Medication adherence at three months of follow-up, n (%)[a]		
VAS score, median (IQR)	95 (88 – 100)	95 (88 – 100)
Low adherent n (%)	25 (2.6)	29 (4.1)
Medium adherent	118 (12.2)	85 (11.9)
Adherent n (%)	825 (85.3)	602 (84.1)

CD: Crohn's disease, UC: ulcerative colitis, SD: standard deviation; IQR: interquartile range: ASA: aminosalicylic acid; Aza: azathioprine; 6MP: 6-mercaptopurine; MTX: methotrexate; TNF: tumour necrosis factor; VAS: Visual Analogue Scale; IQR: interquartile range; CI: confidence interval [a]Measured in patients who take IBD-specific medication

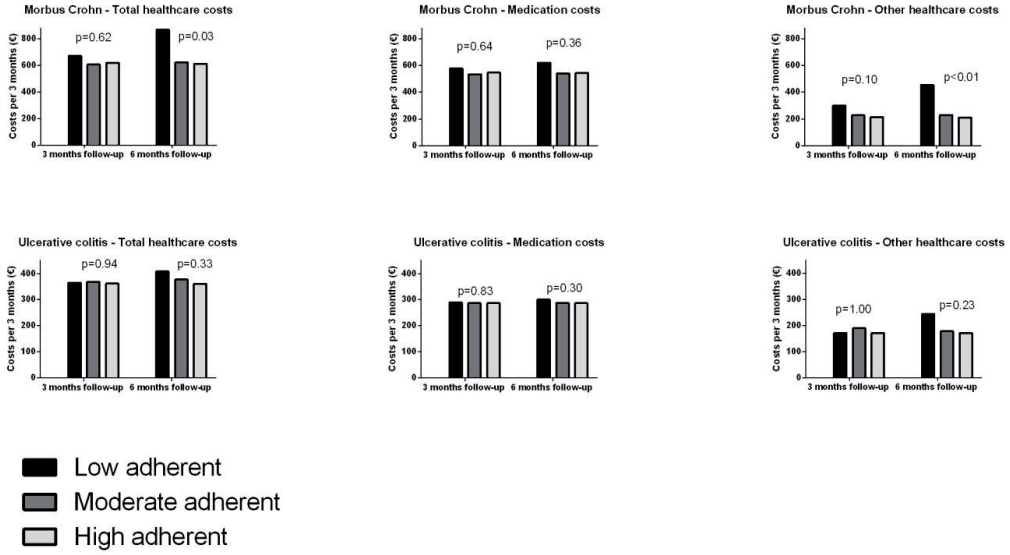

Fig.1: Healthcare costs attributed to (low) adherence in IBD patients, presented in Euros for the year 2015, per 3 months of follow-up

Note: Cost details can be found in Supplementary Table 1. Mean log costs were calculated for each adherence group in our cohort correcting for all covariates (gender, smoking status, age, disease duration and disease activity score) and transformed back to costs in euros.
P-levels represent the difference between high and low adherence

Flares associated with low adherence

Low adherence was not found to be associated with the development of flares after three- or six- months of follow-up in CD. In UC patients, low and moderate adherence was associated with the development of a flare after three months with borderline statistical significance (adjusted Odds Ratio (OR) 1.61 (95% CI 0.78 – 3.32) and 1.41 (95% CI 1.02 – 1.95) respectively, p=0.05 (Table 2).

HrQoL associated with low adherence

In CD, IBDQ and EQ5D-index scores of low adherent patients declined after thee- and six months relative to high adherent patients (not statistically significant) (Table 3). For UC, no association between low adherence and HrQoL was observed.

Covariates and their association with the outcomes

Crohn's disease

a) Healthcare costs. Male gender (p=0.01), shorter disease duration (p<0.01), and lower age (p<0.01) were associated with increased healthcare costs after three and six months of follow-up (Supplementary Table 3).
b) Flares. Higher short-CDAI scores (p<0.01) were associated with flares after three and six months, and current smoking contributed to the development of flares after six months (p=0.08).
c) HrQoL. Female gender (p<0.01), current smoking (p=0.06), and higher short-CDAI-score (p=0.01) were associated with a decrease in IBDQ scores after three and six months of follow-up.

Ulcerative colitis

a) Healthcare costs. Shorter disease duration (p<0.01), higher MTWSI-score (p<0.01), lower age (p<0.01) were associated with higher costs after three and six months of follow-up.
b) Flares. Shorter disease duration (p<0.01) and higher MTWSI scores (p<0.01) were associated with the development of flares after three and six months.
c) HrQoL. Female gender (p<0.01), current smoking (p=0.01), higher MTWSI score (p<0.01), shorter disease duration (p=0.05) and lower age (p=0.06) were associated with a decrease in IBDQ scores after three and six months of follow-up.

Table 2. Flares due to low adherence in IBD patients

	+ 3 months of follow-up			+ 6 months of follow-up		
Medication adherence	Adj. OR	95% CI	P-value	Adj. OR	95% CI	P-value
M. Crohn (n=1002 and n=981)						
Low adherent	0.97	0.52 – 1.81	0.24	1.11	0.52 – 2.38	0.73
Moderate adherent	1.26	0.95 – 1.66		1.09	0.78 – 1.51	
High adherent*						
Ulcerative colitis (n=734 and n=726)						
Low adherent	1.61	0.78 – 3.32	0.05	1.77	0.86 – 3.65	0.21
Moderate adherent	1.41	1.02 – 1.95		0.93	0.64 – 1.36	
High adherent*						

*Adj. OR: Adjusted Odds Ratio; CI: confidence interval. All outcomes were corrected for gender, age, disease duration, smoking status and disease activity score * Reference category*

Table 3. Impact of low adherence on HrQoL in IBD patients

	+ 3 months of follow-up			+ 6 months of follow-up		
Medication adherence	Regression coefficient (β)	95% confidence interval	P-value	Regression coefficient (β)	95% confidence interval	P-value
M. Crohn (n=1,025 and n=981)						
Outcome: IBDQ score						
Low adherent	-2.49	-7.33 – 2.34	0.17	-3.83	-8.76 – 1.09	0.19
Moderate adherent	-1.35	-3.32 – 0.62		-0.79	-2.65 – 1.06	
High adherent*						
Outcome: EQ5D-index score						
Low adherent	-0.01	-0.05 – 0.02	0.37	-0.05	-0.10 – -0.00	0.07
Moderate adherent	-0.01	-0.02 – 0.01		-0.00	-0.02 – 0.02	
High adherent*						
Ulcerative colitis (n=747 and n=726)						
Outcome: IBDQ score						
Low adherent	-0.21	-5.69 – 5.28	0.69	0.42	-5.65 – 6.49	0.45
Moderate adherent	-0.57	-3.07 – 1.94		1.29	-1.14 – 3.72	
High adherent*						
Outcome: EQ5D-index score						
Low adherent	0.03	0.00 – 0.06	0.04	-0.02	-0.06 – 0.02	0.49
Moderate adherent	-0.00	-0.02 – 0.01		0.00	-0.02 – 0.02	
High adherent*						

*All outcomes were corrected for gender, age, disease duration, smoking status *Reference category*

DISCUSSION

In this large prospective cohort study on the longitudinal impact of medication adherence in IBD, we found that low adherence was associated with a substantial increase in healthcare costs in CD patients over time. Low adherence was not found to be associated with the development of flares or a decrease in HrQoL.

Low adherence in CD patients was associated with a 42% increase (+ €255) in total three-monthly healthcare costs spent after six months, which could be attributed to both higher costs of medication use and other healthcare costs such as costs for hospitalizations. Cost outcomes were corrected for gender, smoking, age, disease duration and disease activity scores. Low adherence was not associated with increased costs during six months of follow-up in UC patients, although all cost outcomes were the highest in low adherent patients. Previously, costs of non-adherence have been studied in UC patients treated with 5-ASA compounds,[12,14] and CD and UC patients treated with infliximab.[16,31,32] In these studies, all costs among non-adherent patients were higher compared with those of adherent patients. Another study reported that non-adherent CD patients had worse clinical outcomes at similar aggregate costs compared to adherent CD patients.[33] In our data, we observed that costs of moderate and high adherent CD and UC patients remained about the same after three-and six- months of follow-up, while costs of low adherent CD patients gradually increased over the same period. It is conceivable that the negative effects on the cost profile of patients take longer to manifest. The effects on healthcare consumption seem to be more pronounced in CD patients. In general, healthcare costs of CD patients are three times higher than those of UC patients, however,[17] which may explain why the absolute increase in costs for low adherent CD patients is more pronounced.

We hypothesized that higher cost of low adherent patients were accompanied by an increased risk of flares during follow-up. This appeared not to be the case for CD patients, however. Higher total costs for low adherent CD patients were a result of higher medication- and other healthcare costs, including hospitalizations, diagnostics and outpatient clinic visits. In UC patients, low adherence was associated with the development of flares with borderline statistical significance. Flares were found to be associated with non-adherence in UC patients treated with 5-ASA compounds previously.[9,10] No studies have been published on the association between flares and non-adherence in CD patients. However, non-adherent CD patients treated with infliximab have been reported to have an increased risk for hospitalizations and associated higher costs of healthcare within one year of follow-up,[31] which is in line with our cost results in CD patients. Of note, low adherence has been found to be associated with loss of response in patients using anti-TNF compounds in patients followed for one year.[34]

In our data, we could not deduct an significant association between low adherence and (impaired) HrQoL. In a cross-sectional study on adherence and HrQoL in a Hungarian

population based IBD cohort, no association was observed either.[35] Therefore, medication adherence appears not to be a critical factor impacting HrQoL.[36]

Observational studies on the clinical impact of adherence are prone to confounding. Therefore, extensive correction was applied. Irrespective of the role of adherence, we identified female gender, shorter disease duration, lower age, higher disease activity scores and current smoking to be associated with flares, increased healthcare costs and a decline in HrQoL scores, which is in line with literature.[37–42] Since disease activity is one of the main drivers of healthcare costs,[39] it may be conceivable that the impact of nonadherence on healthcare costs requires a longer follow-up.

Strengths of our study include the prospective design and the large number of patients. This allowed us to study the impact of low adherence longitudinally, and to correct for a several number of covariates. Some aspects of our study warrant comment, however. First, self-report may have led to over- or underestimation of both adherence and cost outcomes. Non-adherence identification can either be based on biological assays,[43] pharmacy refill data[9] or questionnaires.[1] In general, questionnaires tend to have a moderate-to-high concordance with other (more invasive) measures of medication adherence.[44] Previously, we reported that a simple, self-reported VAS scale as used in our studies is highly accurate for assessing adherence in IBD patients when using self-report.[45] Self-reported healthcare consumption and associated calculated costs were found to be highly concordant with medical records in IBD patients.[46] Second, the amount of missing data usually increases over time in cohort studies, which might introduce attrition bias. We opted to reduce the risk of bias by performing multiple imputation techniques, which has been widely accepted for handling missing data.[47] However, residual bias can never be fully excluded. For example, outliers (i.e. patients who consume excessive healthcare or patients who do not incur costs at all), may induce bias in cost outcomes. Lastly, we were not able to study the impact of low adherence on separate units of healthcare consumption with multivariable testing. Since a considerable number of patients reported no costs for several items, distributions of these data were highly skewed, leading to convergence problems during the analyses. Nonetheless, by comparing the mean costs of separate healthcare categories between low and high adherence groups, we observed that low adherence was mainly associated with higher costs for hospitalizations. This might suggest that complications or (ongoing) disease activity, secondary to low adherence, are the main drivers of the increased costs in this group.

In conclusion, this study finds low medication adherence in CD patients to be associated with a substantial increase in healthcare costs over time. Efforts to promote adherence in patients with CD and possibly UC, may help constrain healthcare costs.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Healthcare costs attributed to low adherence in IBD patients, presented per 3 months of followup, in Euros for the year 2015

	+ 3 months of follow-up			+ 6 months of follow-up		
Medication adherence	Mean costs per 3 months of followup (€)	95% confidence interval	P-value	Mean costs per 3 months of followup(€)	95% confidence interval	P-value
M. CROHN (n= 1,166)						
Total healthcare costs						
Low adherent	672	482 - 938	0.62	868	630 – 1,195	0.03
Moderate adherent	605	526 - 694	0.68	623	541 - 717	0.79
High adherent	620	563 - 682	#	613	557 - 675	#
Medication costs						
Low adherent	580	443- 761	0.64	621	461 - 837	0.36
Moderate adherent	535	470 - 609	0.57	542	473 - 622	0.92
High adherent	547	488 - 613	#	545	486 - 611	#
*Other healthcare costs**						
Low adherent	300	200 - 448	0.10	454	277 - 740	<0.01
Moderate adherent	227	194 - 265	0.48	229	194 - 269	0.35
High adherent	214	199 - 230	#	211	196 - 227	#
ULCERATIVE COLITIS (n= 831)						
Total healthcare costs						
Low adherent	365	289 - 462	0.94	408	315 - 530	0.33
Moderate adherent	369	321 - 424	0.76	377	328 - 433	0.42
High adherent	362	327 - 400	#	360	326 - 397	#
Medication costs						
Low adherent	289	256 - 327	0.83	300	262 - 343	0.30
Moderate adherent	287	256 - 321	0.99	288	254 - 328	0.87
High adherent	287	151 - 320	#	287	257 - 319	#
*Other healthcare costs**						
Low adherent	171	105 - 280	1.00	244	137 - 434	0.23
Moderate adherent	190	141 - 258	0.50	178	140 - 225	0.76
High adherent	171	158 - 186	#	171	157 - 186	#

All outcomes were corrected for gender, smoking status, age, disease duration and disease activity score. Euros are calculated for the year 2015, and represent the costs for an average low, medium or high adherent patient concerning all covariates. Of note, patients with €0 costs were not included in these calculations *Including costs for hospitalizations, outpatient clinic visits, surgeries and diagnostics # reference category

Supplementary Table 2. Specification of other healthcare costs of low adherent CD patients, univariable analysis, presented per 3 months of follow-up, in Euros for the year 2015

	+ 3 months of follow-up, mean costs (€)	**+ 6 months of follow-up, mean costs (€)**
	Hospitalization costs	
Low adherent	408	542
Moderate adherent	202	198
High adherent	199	194
	Surgery costs	
Low adherent	9	15
Moderate adherent	9	5
High adherent	9	7
	Diagnostics costs	
Low adherent	54	58
Moderate adherent	36	39
High adherent	39	37
	Outpatient clinic costs	
Low adherent	120	121
Moderate adherent	92	89
High adherent	87	85

Supplementary Table 3a. Multivariable associations between covariates and Log total healthcare costs

	+ 3 months of follow-up			+ 6 months of follow-up		
Medication adherence	Regression coefficient (β)	95% confidence interval	P-value	Regression coefficient (β)	95% confidence interval	P-value
			M. CROHN			
Female versus male gender	-0.26	- 0.45 - - 0.08	0.01	-0.26	- 0.45 - - 0.08	0.01
Smoking status						
Current	0.10	-0.15 – 0.35	0.43	0.09	-0.15 – 0.35	0.45
Previous	0.01	-0.19 - 0.22	0.90	0.01	-0.19 - 0.22	0.91
Never*						
Disease duration (per year)	-0.01	-0.02 - 0.01	<0.01	-0.01	-0.02 - 0.01	<0.01
Short-CDAI score (per point)	<0.01	-0.00 - 0.00	0.09	<0.01	-0.00 - 0.00	0.08
Age (per year)	-0.02	-0.02 -0.01	<0.01	-0.02	-0.02 -0.01	<0.01
			ULCERATIVE COLITIS			
Female versus male gender	-0.02	-0.14 - 0.11	0.77	-0.02	-0.14 - 0.11	0.77
Smoking status						
Current	0.01	-0.28 - 0.30	0.96	0.01	-0.28 - 0.30	0.97
Previous	-0.11	-0.25 - 0.02	0.10	-0.11	-0.25 - 0.02	0.11
Never*						
Disease duration (per year)	-0.02	-0.02 -0.00	<0.01	-0.01	-0.02 -0.00	<0.01
MTWSI score (per point)	0.07	0.05 - 0.10	<0.01	0.07	0.05 - 0.10	<0.01
Age (per year)	-0.01	-0.01 -0.00	<0.01	-0.01	-0.01 -0.00	<0.01

*Reference category CDAI: Crohn's Disease Activity Index; MTWSI: Modified Truelove and Witts Index

Supplementary Table 3b. Multivariable associations between covariates and flares

	+ 3 months of follow-up			+ 6 months of follow-up		
Medication adherence	Adjusted Odds Ratio	95% confidence interval	P-value	Adjusted Odds Ratio	95% confidence interval	P-value
M. CROHN						
Female versus male gender	0.82	0.63 – 1.06	0.13	0.88	0.67 – 1.16	0.37
Smoking status						
Current	1.14	0.92 – 1.89	0.13	1.40	0.96 – 2.06	0.08
Previous	1.19	0.89 – 1.59	0.24	1.27	0.94 – 1.73	0.12
Never*						
Disease duration (per year)	0.99	0.98 – 1.00	0.23	1.00	0.99 – 1.01	0.78
Short-CDAI score (per point)	1.01	1.00 – 1.01	<0.01	1.04	1.00 – 1.01	<0.01
Age (per year)	1.01	0.99 – 1.01	0.31	1.01	1.00 – 1.02	0.21
ULCERATIVE COLITIS						
Female versus male gender	1.03	0.78 – 1.35	0.84	1.08	0.82 – 1.44	0.57
Smoking status						
Current	1.16	0.60 – 1.72	0.95	1.10	0.64 – 1.91	0.71
Previous	0.87	0.65 – 1.17	0.36	0.82	0.61 – 1.10	0.20
Never*						
Disease duration (per year)	0.98	0.96 – 0.99	<0.01	0.98	0.97 – 0.99	0.01
MTWSI score (per point)	1.30	1.22 – 1.39	<0.01	1.17	1.08 – 1.26	<0.01
Age (per year)	0.99	0.98 – 1.00	0.26	0.99	0.98 – 1.01	0.33

*Reference category CDAI: Crohn's Disease Activity Index; MTWSI: Modified Truelove and Witts Index

Supplementary Table 3c. Multivariable associations between covariates and IBDQ

	+ 3 months of follow-up			+ 6 months of follow-up		
Medication adherence	Regression coefficient (β)	95% confidence interval	P-value	Regression coefficient (β)	95% confidence interval	P-value
M. CROHN						
Female versus male gender	-7.41	-10.67 - -4.16	<0.01	-7.41	-10.67 - -4.15	<0.01
Smoking status						
Current	-4.47	-9.09 – 0.15	0.06	-4.48	-9.10 – 0.14	0.06
Previous	2.62	-1.01 – 6.25	0.16	2.61	-1.02 – 6.24	0.16
Never*						
Disease duration (per year)	-0.10	-0.23 – 0.03	0.14	-0.10	-0.23 – 0.03	0.13
Short-CDAI score (per point)	-0.03	-0.05 - -0.01	0.01	-0.03	-0.05 - -0.01	0.01
Age (per year)	-0.11	-0.25 – 0.02	0.09	-0.12	-0.25 – 0.01	0.08
ULCERATIVE COLITIS						
Female versus male gender	-6.26	-9.54 - -2.98	<0.01	-6.27	-9.55 - -2.98	<0.01
Smoking status						
Current	-6.19	-13.47 – 1.08	0.10	-6.27	-13.5 – 1.01	0.09
Previous	4.30	0.87 – 7.73	0.01	4.28	0.84 – 7.72	0.01
Never*						
Disease duration (per year)	0.16	-0.00 – 0.32	0.05	0.16	-0.00 – 0.32	0.05
MTWSI score (per point)	-1.62	-2.20 - -1.04	<0.01	-1.62	-2.20 - -1.04	<0.01
Age (per year)	0.13	-0.01 – 0.26	0.06	0.13	-0.00 – 0.27	0.06

*Reference category CDAI: Crohn's Disease Activity Index; MTWSI: Modified Truelove and Witts Index

CHAPTER 5

Future developments and general discussion

CHAPTER 5.I

The economic impact of the introduction of biosimilars in inflammatory bowel disease

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) entails a high economic burden to society. We aimed to estimate the current and future impact of the introduction of biosimilars for infliximab on IBD-related health care costs.

Methods: We designed a stochastic economic model to simulate the introduction of biosimilars in IBD, using a 5-year time horizon, based on the Dutch situation. Prevalence data on ulcerative colitis (UC) and Crohn's disease (CD) and IBD-related health care costs data were used as input. Assumptions were made on price reductions of anti-tumour necrosis factor (TNF) therapy, increase of anti-TNF prescription rate, and development of hospitalization costs. The base case scenario included a gradual decrease in prices of biosimilars up to 60%, a gradual decrease in prices of original anti-TNF compounds up to 50%, and an annual increase of anti-TNF prescription rate of 1%, and this was compared with no introduction of biosimilars. Sensitivity analyses were performed.

Results: For the base case, cost savings over the total of 5 years were on average €9,850 per CD patient and €2,250 per UC patient, yielding in €493 million total cost savings (a reduction of 28%) for The Netherlands. Results were predominantly determined by price reduction of anti-TNF therapy, threshold price reduction at which physicians switch patients towards biosimilars and the extent to which switching will take place.

Conclusions: The introduction of biosimilars for infliximab can be expected to have a major impact on the cost profile of IBD. The economic impact will depend on local pricing, procurement policies and the physician's willingness to switch patients to biosimilars.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic intestinal disorders comprising Crohn's disease (CD) and ulcerative colitis (UC). In Europe, the incidence rates are currently estimated to be 6.3 per 100 000 person-years for CD and 9.8 per 100 000 person-years for UC.[1,2] IBD is associated with a high economic burden to society;[3] the mean annual IBD-related health care costs in CD and UC in 2011 were estimated at €6,500 and €2,400, respectively.[4] The anti-tumour necrosis factor (TNF) compounds infliximab and adalimumab were identified as the main cost drivers in IBD, accounting for 61% of annual IBD-related health care costs[.4–6] The proportion of costs for anti-TNF prescriptions is still increasing, but this is compensated by a decrease in costs for hospitalizations.[5,7]

Infliximab biosimilars, which are copy versions of currently licensed anti-TNF therapy, have been approved by the European Medicines Agency for the treatment of CD and UC, and have now entered the market. The patent on Remicade® has expired.[8] The anticipated price reduction of biosimilars relative to the prices of the originators is expected to have a major impact on the cost profile of IBD in the next few years.[9,10] In addition to the lower prices of biosimilars, the price of the originator can be expected to respond, although to a lesser extent, to the advent of these competing agents as well, which might consequently result in a change in prescription behaviour of anti-TNF therapy.

The aim of the present study was to estimate the current and future impact of the introduction of anti-TNF biosimilars on IBD-related direct health care costs in The Netherlands.

METHODS

Model design

We designed a stochastic economic probabilistic model to simulate the impact of the introduction of anti-TNF biosimilars on annual IBD-specific health care costs in The Netherlands, compared with no biosimilar introduction (the reference case). The model was built in Microsoft Excel 2010, using @Risk, an add-in (Pallisade Corporation @Risk v5.5, Ithaca, NY, USA) to perform analyses using Monte Carlo simulation techniques. Simulations were based on the Dutch situation, including Dutch prevalence data on UC and CD and Dutch IBD-related health care costs data. Assumptions had to be made on: 1) price reductions of anti-TNF therapy; 2) future development of increasing anti-TNF therapy prescription rates; and 3) development of hospitalization costs over time. The starting year was 2014. The time horizon modelled was 5 years. Health care costs for the years 2015 up to 2019 were simulated assuming: 1) no introduction of biosimilars (i.e. reference case); and 2) introduction of biosimilars. For each simulation, 50 000 runs were conducted.

Model assumptions

Prevalence of IBD

Based on the Vektis database[8] (centre for information and standardization for insurance companies), which consisted of patients with at least one 'Diagnosis Treatment Combination' of IBD between 2008 and 2012 and alive on December 31, 2012,9 we estimated the number of Dutch adult IBD patients in 2014 to be 85 400 (equaling 507 patients per 100 000 inhabitants, 55% UC and 45% CD patients), see Table 1. These estimations were assumed to remain stable over the next 5 years.1

Health care costs

Health care costs and prescription rates of anti-TNF therapy were extracted from the COIN study.[4] In short, the COIN-study enrolled more than 3000 Dutch IBD patients who were prospectively followed by means of 3-monthly detailed questionnaires on health care utilization (for full details see reference 4). For the current study, the most recently published 2-year follow-up data were used[5] and costs were updated to euros for the year 2014 (the starting year of the simulation) using Dutch consumer price indexes (CPI).[11] Health care costs were modeled as: 1) costs for Remicade® use (price based on average weight of 75 kg and 1.8 infusions per 3 months); 2) costs for Humira® use (prices based on 6.5 injections per 3 months (81% administered adalimumab 40 mg per 2 weeks) or 13 injections

per 3 months (19% of patients administered adalimumab 80 mg per 2 weeks)); 3) costs for biosimilar use; 4) hospitalization costs (including cost price per day spent on the medical ward of either a general hospital, an academic hospital or an intensive care unit, multiplied by the number of days admitted); and 5) remaining health care costs (including costs for medications others than anti-TNF compounds, diagnostic procedures, outpatient clinic visits and IBD-specific surgery) (see Table 1, and details on unit prices of resource use in the COIN study (see Supplementary Table 1).[12,13] Annual costs for Remicade® use, Humira® use and biosimilar use were calculated by multiplying simulated annual prescription rates with simulated annual unit prices. Hospitalization costs were assumed to decrease over time.[5,7] Other health care consumptions were assumed to remain stable over time. Health care unit prices for the years 2015–2019 were simulated as real-time prices and were corrected for inflation, using the average annual observed consumer price index (CPI) of health care for the years 2005–2015.[11] Only medication prices were assumed to remain stable (i.e. no inflation), according to the findings of recent years.[11]

Table 1. Assumptions regarding prevalence, health care costs and use of anti-TNF compounds in IBD patients in 2014.

Variable	Model input	-Source/assumption/explanation
Prevalence		
Dutch prevalence of IBD; adult patients	IBD cases: 85,400 55% UC and 45% CD	Based on Vektis database[31]: number of patients with at least one 'Diagnosis Treatment Combination' of IBD between 2008 and 2012, and alive on December 31, 2012[32]; assumed to remain stable over time[1+22]
Anti-TNF use		
Percentage of IBD patients using	CD: Remicade® 10%, Humira® 13%	[5]
anti-TNF compounds in 2014	UC: Remicade® 3%, Humira® 2%	
Annual costs		
Annual average health care costs/ patient, in euros for the year 2014, whereof	€/CD patient €/UC patient	Extracted from the COIN study[4,5] and updated for the year 2014 using Dutch consumer price indexes[33]
costs for Remicade® use	€ 2,025 € 633	
costs for Humira® use	€ 2,258 € 285	
costs for biosimilar use	€ 0 € 0	Including diagnostic procedures, outpatient clinic visits, surgeries and medication use other than
hospitalization costs	€ 802 € 340	
costs of remaining health care utilization	€867 € 1,069	anti-TNF compounds

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; TNF, tumour necrosis factor.

Reference case

The reference case represented the situation with no introduction of biosimilars for infliximab. In this simulation, the 2014 situation was maintained. Thus, neither anti-TNF prescription rates, nor hospitalization consumptions nor other health care consumptions were assumed to change over time. Correction was only applied for price inflation for the years 2015 up to 2019.

Base case scenario

When simulating the introduction of biosimilars, additional assumptions had to be made. In order to substantiate these assumptions, we presented different future scenarios to an expert panel of 15 gastroenterologists with expertise on IBD, employed in seven academic and six general Dutch hospitals. Based on the combined responses of this expert panel, the

Table 2. Model input for the base case scenario, in addition to the general assumptions.

Variable	Model input	Source/assumption/explanation
	anti-TNF (use and prices)	
Use of anti-TNF compounds 2015-2019	Linear increase of minimum, most likely and maximum 1%, 1% and 2%/year (modelled as Pert-distribution)	Source: expert panel (Supplementary Table 1), (5)and (8); resulting in a total increase of minimum, most likely and maximum 5%, 5% and 10% respectively over the simulated period 2015 - 2019
Subtype of anti-TNF compounds in new anti-TNF users	Humira®: 20% Infliximab: 80% Remicade®: 20% biosimilars: 80%	Assumptions
Biosimilar price in relation to Remicade® price of the year 2014[a]	Pert(9) (30%. 40%, 60%), and modelled as a gradually, exponential decrease in price	Source: Supplementary Table 1. The numbers are presented as the residual percentages of the original price. This price reduction was assumed to be quickly reached (modelled as an exponential function) after biosimilar introduction
Remicade® price in relation to Remicade® price of the year 2014[a]	Pert (40%, 50%, 70%), and modelled as a gradually, linear decrease in price	Source: expert panel (Supplementary Table 1). This price reduction was assumed to be reached linearly after biosimilar introduction
Humira® price in relation to Humira® price of the year 2014[a]	Pert (40%, 50%, 90%), and modelled as a gradually, inverse exponential decrease in price	Source: expert panel (Supplementary Table 1) This price reduction was assumed to be reached slowly (modelled as an inverse exponential function) after biosimilar introduction
Remicade® and Humira® users switching to biosimilars		Source: expert panel (Supplementary Table 1)
Applicable when biosimilars are less than…% of the original price	Pert (30%, 50%, 80%)	
When this threshold price reduction is reached, …% of Remicade® and Humira® will switch to biosimilars	Uniform (80%, 85%), gradually reached	
	Hospitalizations and other healthcare consumptions	
Development of hospitalization consumption 2015-2019	Uniform (0%, 10%)	Assuming no (0%) up to moderate decline of maximum 10% in five years' time (5)
Development of other healthcare costs 2015-2019	No further increase or decrease	Assuming other healthcare consumptions to remain stable over the next five years. Only price inflation correction was applied (5)

TNF, tumour necrosis factor.
[a]prices for biosimilars, Remicade® and Humira® were assumed to be highly correlated (r = 0.95).

base case scenario was defined (Table 2). (For full details see Supplementary Table 2.) The assumptions in the base case scenario included:

1. The use of anti-TNF compounds will continue to increase annually by 1% (with a minimum of 1% and a maximum of 2%(modeled with Pert distribution[14])), which is in line with the observed increase in the use of anti-TNF compounds in the COIN study[5] and the steady increase of anti-TNF volume over the years 2006–2014.[15]
2. Since biosimilars will be cheaper than the originators, we assumed that biosimilars will preferentially be prescribed in anti-TNF naïve patients, although a subset of patients can be expected to be initiated on a subcutaneous alternative, such as Humira®. We therefore assumed that 20% of new anti-TNF users will start on Humira® and 80% on infliximab (80% biosimilars and 20% Remicade®).
3. The expert panel expected that, due to price competition, the price of biosimilars will be considerably lower than the 2014 price of Remicade®, with a plateau of 40% of the original price reached after 5 years and with a minimum of 30% and a maximum of 60%, modelled as an exponential decrease (see Fig. 1). This estimate seems to be a reliable prediction based on recent pricing of biosimilars in The Netherlands.
4. The expert panel expected Remicade® and Humira® to remain more expensive than biosimilars over time. However, the manufacturers of these compounds were expected to respond to the market entry of biosimilars (price competition) by gradually reducing their prices towards 50% of the original price with a minimum of 40% and a maximum of 70% in Remicade® and a minimum of 40% and maximum of 90% in Humira® (Pert distribution) (concerning real purchasing prices). Humira® prices were assumed to decrease more slowly, because no direct competitor of this compound is presently

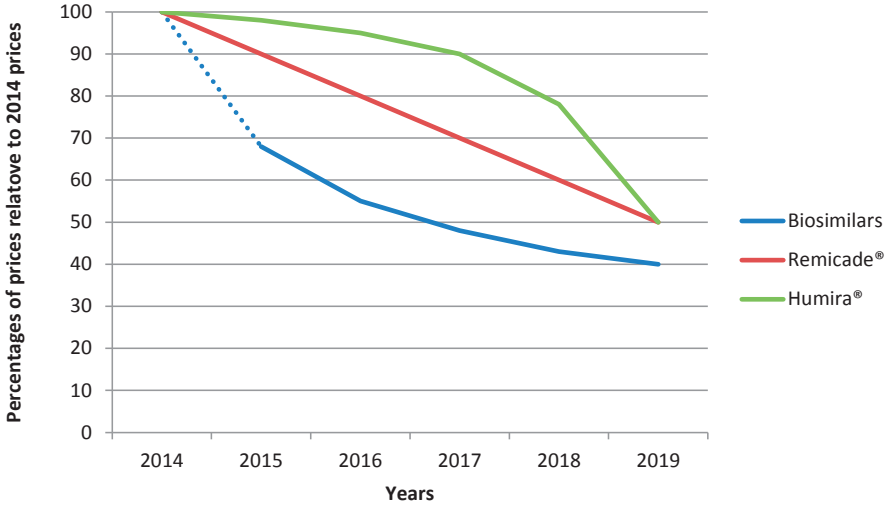

Fig. 1: Expected development of anti-TNF compound prices in 2015-2019 relative to 2014 prices due to the introduction of biosimilars (base case scenario).

available on the market. The expected price development of biosimilars, Remicade® and Humira® are depicted in Fig. 1. In order to account for the fact that prices of biosimilars, Remicade® and Humira® are interrelated, the simulated prices were modelled to be highly correlated (r = 0.95). This means that when, for example in one of the iterations, the price for biosimilars is drawn out of the middle of the underlying distribution, then the other two prices will be drawn out of the middle, out of their underlying distributions as well.

5. Concerns regarding efficacy and safety of newly introduced biosimilars caused the expert panel to expect a relative high price reduction of 50% (minimum 30% and maximum 80%, Pert distribution) necessary to induce a switch to biosimilars in anti-TNF users. When this threshold price reduction would be reached, a minimum of 80% and maximum of 85% (uniformly distributed) of anti-TNF users would be expected to gradually switch towards biosimilar therapy. Furthermore, it was assumed that in many hospitals, switching anti-TNF users to biosimilar therapy would be an active process, forced by regulatory arrangements in the organization.
6. Hospitalization costs were assumed to decrease gradually over time with a minimum of 0 and a maximum of 10% reduction compared with the year 2014, modelled with uniform distribution.

Sensitivity analyses

One-way sensitivity analyses were conducted to test the robustness of our model (see Table 3). In each analysis, one of the components was adjusted relative to the base case scenario, and all other variables remained unchanged. Parameters that were varied in the sensitivity analyses included: a) a higher market uptake of anti-TNF compounds (+10% in 5 years); b) new infliximab users all starting on biosimilars (100%); c) immediate maximum price reduction of biosimilars; d) a range of price reductions of anti-TNF therapy (between 20% and 70%); e) physicians switching towards biosimilar therapy on high or low price reductions of biosimilars (70% - 5%); f) only a small, or a large, proportion of patients switching towards biosimilar therapy once threshold prices are reached (5/10%90/100%); and g) Remicade® and Humira® not reducing their prices after biosimilar market entry.

Outcomes

Health care costs for the reference case, the base case and the different sensitivity analyses were presented per CD or UC patient, for the total Dutch IBD population, per 100 000 inhabitants for the different years (2014–2019) and as sum over the total simulated period of 5 years. The differences in health care costs between scenarios and the reference case represented the economic impact of the introduction of biosimilars.

Table 3. Sensitivity analysis

Sensitivity analysis, Nr.	Assumption/point estimation/distribution	Explanation
1) Use of anti-TNF compounds 2015-2019	Most likely increase over 5 years of 10% *(vs. 5%)*	Impact of high market uptake anti-TNF compounds due to decline in prices
2) Subtype of anti-TNF compounds in new anti-TNF users	Humira®: 20% Infliximab: 80% Remicade®: 0% *(vs. 20%)* biosimilars: 100% *(vs. 80%)*	Impact of new infliximab users to all start with biosimilar therapy
3) Biosimilar price in relation to Remicade® price of the year 2014	Price difference immediately reached *(vs. gradually)*	Impact of immediate maximum price reduction of biosimilars
4) Anti-TNF price in relation to Remicade® price of the year 2014	Modelled as a range of point estimators from 80% to 30% *(vs. Pert (30%. 40%, 60%) for biosimilars, Pert (40%, 50%, 70%) for Remicade® and Pert (40%, 50%, 90%) for Humira®)*	Impact of a range in price reduction of anti- TNF therapy (including biosimilars, Remicade® and Humira®), starting with 20% reduction (80% remaining of price of originator in 2014) up to 70% reduction (30% remaining of price of originator in 2014)
5) Remicade® and Humira® price in relation to 2014 prices	100% *(vs. Pert (40%, 50%, 70%) for Remicade® and Pert (40%, 50%, 90%) for Humira®)*	Impact of no price reductions of Remicade® and Humira® after introduction of biosimilars
6) Remicade® and Humira® users switching to biosimilars		
6A)Applicable when biosimilars are less than …% of the original price	95% *(vs. Pert (30%, 50%, 80%))*	Impact of physicians switching to biosimilars on even a very small price reduction
6B)Applicable when biosimilars are less than …% of the original price	30% *(vs. Pert (30%, 50%, 80%))*	Impact of physicians only switching to biosimilars on a high price reduction
6C) When the threshold price reduction is reached,…% of Remicade® and Humira® will switch to biosimilars	Uniform (5%, 10%) *(vs. Uniform (80%, 85%))*	Impact of only a small proportion of patients switching to biosimilars when the threshold price reduction of reached
6D) When the threshold price reduction is reached,…% of Remicade® and Humira® will switch to biosimilars	Uniform (90%, 100%) *(vs. Uniform (80%, 85%))*	Impact of a large proportion of patients switching to biosimilars when the threshold price reduction is reached

TNF: tumour necrosis factor

RESULTS

Base case compared with reference

In the base case scenario, the introduction of biosimilars for anti-TNF resulted in gradual inclining cost savings towards a total of €9,850 per CD patient and €2,250 per UC patient over the simulated 5 years, equaling a 33% and 19% reduction in total costs per patient, respectively (Table 4). In the base case, the introduction of biosimilars yielded total health care savings of €493 million over the total 5 simulated years after the introduction in The Netherlands, equaling a 28% reduction in total costs (Fig. 2). Cost savings reached €2.93 million per 100 000 inhabitants within the total 5 years. The percent-age of the mean annual costs of anti-TNF compounds relative to the total health care costs declined from 62% to 18%. Detailed results of the base case scenario are presented in Supplementary Table 3.

Sensitivity analyses

In Figure 3, a Tornado graph is depicted, including the components to which the economic impact of the introduction of biosimilars would be most sensitive. The economic impact was influenced mostly by price reductions of anti-TNF therapy, but was also subject to the prescription behaviour of the physician. If physicians would switch to biosimilars in case of only limited relative price reductions, an additional €121 million could be saved as compared with the base case scenario. Conversely, if switching to biosimilars only occurred after large price reductions, cost savings could be expected to be substantially lower. The amount of switching towards biosimilars, once the threshold price reduction was reached, would also influence the final economic impact but to a lesser extent. Even in the case that price reductions would cause a market uptake of biologics of 10% in 5 years instead of a steady market growth of 5%, total cost savings over 5 years would reach €472 million. Mean total cost savings per alternative scenario are presented in Supplementary Table 4.
In Figure 4, a range in potential anti-TNF price reductions is depicted with corresponding total cost savings over 5 years for the Dutch IBD population. Larger price reductions were associated with higher corresponding cost savings.

Table 4. Mean results of the reference [no biosimilars] and base case scenario and simulated differences for the separate years and for the total simulated period.

	2014	2015	2016	2017	2018	2019	In 5 years (total)
IBD-specific health care costs per CD patient (mean, €)							
Reference	5,950	5,960	5,970	5,980	5,990	6,000	29,900
Base case	5,950	5,710	5,010	3,900	2,990	2,450	20,000
Difference	-	-250	-970	-2,080	-3,000	-3,550	-9,850
IBD-specific health care costs per UC patient (mean, €)							
Reference	2,330	2,330	2,340	2,350	2,380	2,360	11,800
Base case	2,330	2,250	2,100	1,870	1,690	1,590	9,500
Difference	-	-81	-240	-480	-670	-770	-2,250
IBD-specific health care costs per IBD patient (mean, €)							
Reference	3,960	3,970	3,970	3,980	3,990	4,000	19,900
Base case	3,960	3,810	3,410	2,780	2,280	1,980	14,200
Difference	-	-160	-570	-1,200	-1,720	-2,020	-5,700
Health care costs for the total Dutch IBD population (mean, € in millions)							
Reference	344	345	346	346	347	348	1,732
Base case	344	331	296	242	198	172	1,239
Difference	-	-14	-49	-105	-149	-176	-493
Cost difference per 100 000 population[33] (mean, € in millions)[a]							
Difference	-	-0.08	-0.29	-0.62	-0.89	-1.05	-2.93
Percentage of costs of anti-TNF/total health care costs in IBD patients (mean, %)							
Reference	61	61	61	61	61	61	
Base case	61	60	55	44	29	18	

In The Netherlands, switching from originator to biosimilar is regulated at local level. The health budget is decided on in consultations between insurance com-panies and hospitals. Local choices regarding prices of biologic therapy are negotiated between hospitals and pharmaceutical companies.

A specification of medians and 90% confidence intervals of the base case scenario can be found in Supplementary Table 3. Reference represents no introduc-tion of biosimilars for anti-TNF therapy.

TNF, tumour necrosis factor; IBD, nflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitits.

[a]Calculated for the Dutch population in 2014: 16 829 inhabitants. Costs were rounded to three digits. Of note, negative costs represent cost savings.

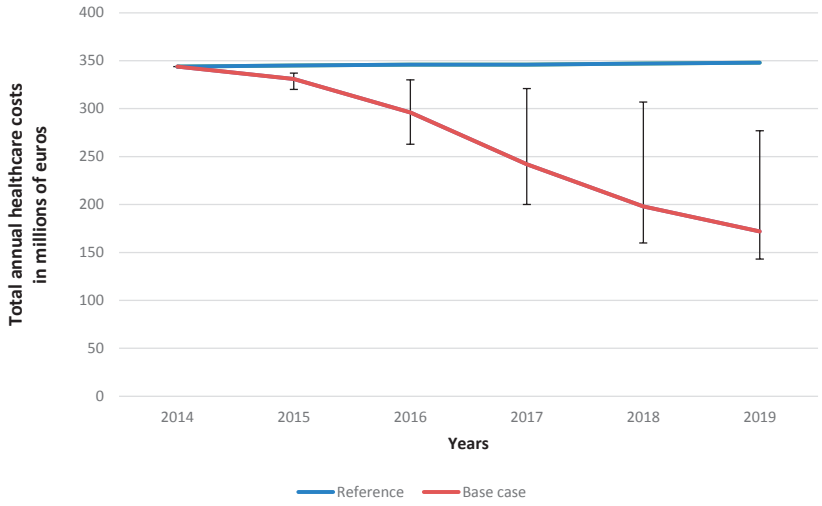

Fig. 2: Development of total annual healthcare costs of Dutch IBD population according to the base case scenario over the years 2014-2019 (mean euros, presented in millions).
Error bars represent 90% confidence intervals of the mean

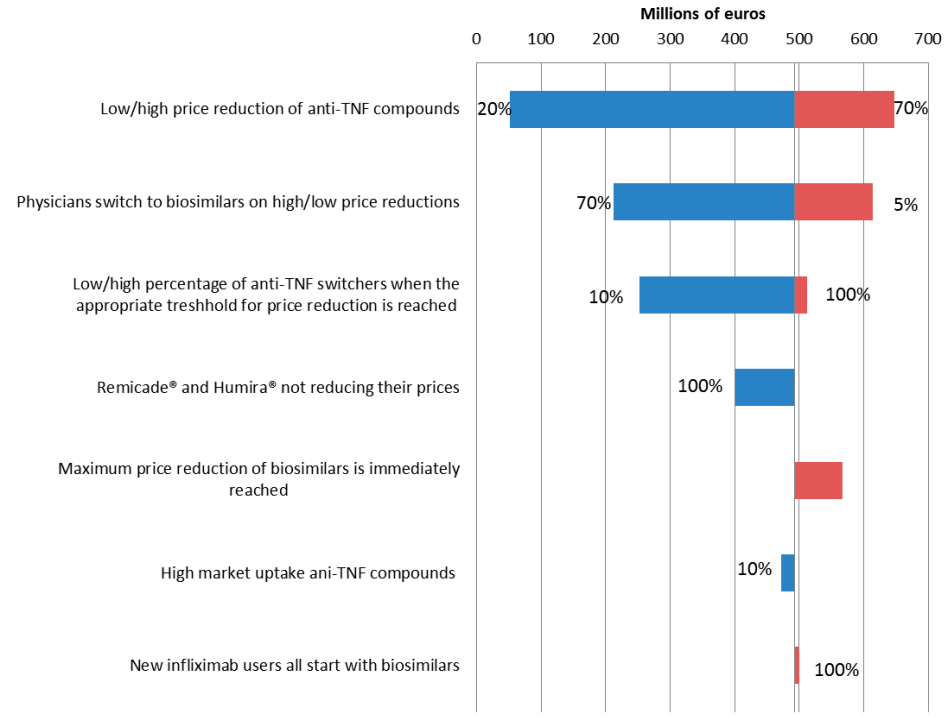

Fig. 3: Sensitivity analyses in comparison to base case results.

Alternative scenario-analyses depicted in a Tornado diagram. The x-axis shows the effect of changes in selected variables on the total cost savings relative to the Base case scenario. The y-axis shows the model parameter that was varied. The bars indicate the change in total cost savings caused by changes in the value of the indicated variable holding all other parameters similar.

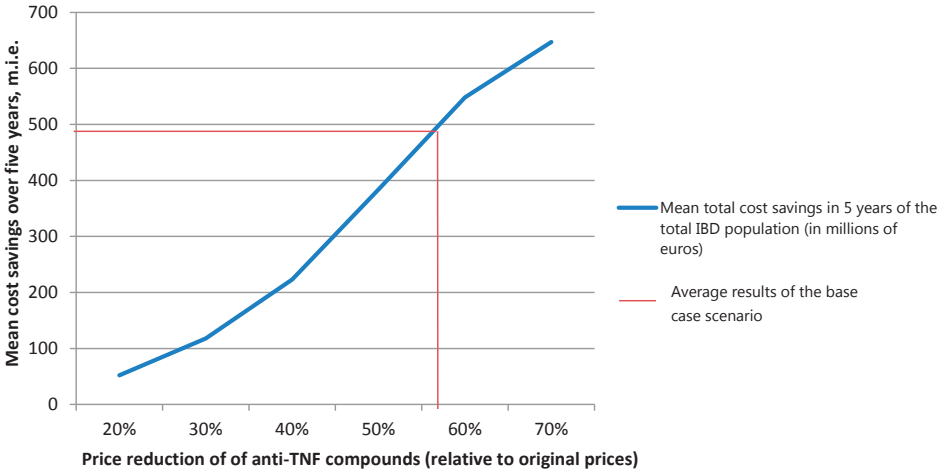

Fig. 4: Mean cost savings over five years for different price reductions of all anti-TNF compounds.

Including equal price reductions of biosimilars, Remicade® and Humira®, with the assumption of exponential price decline in biosimilars, a linear price decline in Remicade® and an inverse price decline of Humira®

DISCUSSION

This study showed that the introduction of biosimilars for infliximab results in substantial savings for IBD-specific health care costs within the first few years. For the Dutch IBD population, total cost savings may amount to €493 million within 5 years after the intro- of biosimilars (equaling a reduction in 28% of total health care costs and €2.93 million cost savings per 100 000 inhabitants). The economic impact of biosimilars is most sensitive to the factual price reductions of anti-TNF therapy, but also depends highly on the threshold price reduction from which physicians switch patients towards biosimilars, and on the extent to which switching takes place once threshold prices are reached.

Over the past few years, multiple different biosimilars have been introduced, of which biosimilars for infliximab were the first to be approved in the field of gastroenterology.[9,16] Price reductions between 10% and 35% have previously been observed,[9] but actual implemented price reductions are uncertain, since data on prices only represent ceiling prices. Non-transparent pricing, due to contracting with hospitals, can lead to large price fluctuations which will not be publicly available.[15] Three budget impact studies have recently been performed: for biosimilars for infliximab; for the treatment of CD in eastern European countries[17]; for the treatment of autoimmune diseases in five European countries[18]; and for the treatment of rheumatoid arthritis in central and eastern European countries.[19] These studies all projected significant cost savings. Concerning eastern European countries, it is mentioned[17] that the introduction of biosimilars may offset the inequity in access to biologic therapy for CD between central and eastern European countries. Concerning the studies performed in central and Western Europe,[18,19] we made some methodological choices that are different compared with those of the previous models: 1) additional to drug-related costs, we added costs for hospitalizations, surgeries, diagnostics and outpatient clinic visits; 2) we projected a longer time horizon of 5 years instead of 1 and 3 years; 3) we added Humira® therapy as a significant market competitor; 4) we added price reductions of the originators as a response to the introduction of the new competitors; and 5) in contrast with previous studies, we did not presume a steady state of the potential market for biosimilars. With respect to the latter argument, the assumption that the introduction of biosimilars, accompanied by a reduction in prices, will only lead to a shift from the use of originators to biosimilars may not be realistic. We argue that the availability of lower-priced biosimilar versions of anti-TNF may lead to a reappraisal of current treatment algorithms, potentially resulting in an increase of top-down strategies in IBD patients.[20] Therefore, the number of users might increase beyond trend as prices fall.[21]

In the two previous budget impact studies on biosimilar-infliximab market entry,[18,19] modest price reductions of maximum 30% were modelled. Although we included a range of possible price reductions in the sensitivity analyses of our study, our base case scenario was based on increasing price reductions towards 60% for biosimilars and 50% for Remicade®

and Humira®. However, it might take time to reach these price reductions, as assumed in our model, so that initial price reductions in the first years after the introduction of biosimilars are comparable to those of previous studies. Irrespective of considerable differences regarding the design of our study, the main findings are fairly similar: the entrance of biosimilars for infliximab is projected to cause substantial cost savings for the health care system.

Several assumptions were required in order to simulate our results. For example, we assumed the incidence rate of IBD to remain stable. Furthermore, population ageing was not taken into account. We do not expect population ageing to influence IBD-specific health care costs within the next 5 years, because the average costs incurred by elderly IBD patients are considerable lower than those incurred by younger patients.[12,22–24] As input in our model, we considered the health care costs as calculated in the COIN study representative for the domain of our study. Patients of the COIN study were derived from seven academic and seven general hospitals, and data were obtained during more than 2 years of follow-up. The validity of the self-report method used in this study was underscored by our recent study, in which we showed that calculated costs are highly concordant with data from the electronic patient record.[25] Moreover, we previously assessed the representativeness of the COIN study by performing a non-responder study and could not detect major differences in demographic or disease characteristics between responders and non-responders.[4] Therefore, we believe that these data are largely generalizable to the whole Dutch IBD population. Furthermore, we assumed a decrease in IBD-related hospitalizations over the next few years. This assumption is in line with observations from several studies, and has been ascribed to an increase in anti-TNF prescription rates.[5,7] The use of anti-TNF compounds was projected to increase with 5% over the next few years, extrapolated from an annual increase of 1% over 2 years of follow-up in the COIN study.[5] This increase may be attributed to the fact that a plateau of anti-TNF use has still not been reached in IBD.15 We feel that a market uptake up to 13%, as calculated in previous studies,[18,19] might however be overestimated.

Second to the direct effect of price reductions of anti-TNF compounds, both the prescription behaviour and the procurement policies regarding switching of patients will substantially affect total health care costs. In the base case scenario, high price reductions were required for a physician to switch towards biosimilars. However, once concerns regarding interchangeability, safety and effectiveness of biosimilars are eliminated, barriers towards switching patients may diminish.[26,27] Substitution of originator for biosimilar is regulated at the country level and, due to local budget, policies regarding substitution will differ as well.[28]

In the following years, many biosimilars are expected to enter the market.[29] Corresponding price reductions may force pharmaceutical companies to lower prices of originators and therapies which share the market. Substantial cost savings can therefore be anticipated and biologics may become available for a larger number of patients. In this era of rapidly changing treatment options, the findings of our study are highly relevant and may contribute to a

better understanding of future developments. Since real purchasing prices of biologics and biosimilars are not publicly accessible, the components of our model and the corresponding outcomes provide clarity and transparency on this subject.

Other strengths of this study include the specification of the economic impact of the introduction of biosimilars for IBD-related health care, including not only costs directly related to the medication, but also IBD-specific hospitalizations, outpatient clinic visits and surgeries. Our model included various aspects of the market entry of a biosimilar, including price reductions, the potential market uptake, competition with adalimumab therapy, prescription behaviour and switching policies. Moreover, as cost savings are presented per 100 000 inhabitants, our results can be extrapolated to other countries. However, there are limitations to our analysis that war-rant comment. Our model is founded on several assumptions (e.g. for price reductions), resulting in the introduction of uncertainty and translating into broad confidence intervals. Furthermore, we did not include more infliximab biosimilars that are yet to be introduced, the market uptake of novel biologics such as integrin antagonists[30] or the introduction of biosimilars for Humira®, of which the patent is due to expire within the next few years.[8] The emergence of these biosimilars can be expected to cause a similar shift in the cost profile in IBD, hence a further reduction of anti-TNF related costs.

In summary, IBD entails a high economic burden to society, which is predominantly determined by the use of biologics. The introduction of biosimilars for infliximab can be expected to result in substantial cost reductions for IBD-related health care. In turn, anti-TNF therapy may become available for a larger number of patients.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Unit prices of resource use in the COIN-study, expressed in 2014 euros

	Unit price (€) Cost price per visit	**References**
Outpatient clinic consultations		
District hospital	68.52	(1)
University medical centre	138.11	(1)
Emergency room	161.66	(1)
General practitioner		(1)
Visit (day-time)	29.98	(1)
Home visit (day-time)	46.04	(1)
Visit (weekend/ night-time)	86.92[a]	(1)
Home visit (weekend/ night-time)	130.38[a]	(1)
	Cost price per hour	
IBD or stoma nurse – per hour	47.17	(1)
Dietician – per hour	51.62	(1)
Hospitalisation	Cost price per day	
Medical ward		
General hospital	465.71	(1)
University medical centre	615.60	(1)
Intensive care unit	2337.12	(1)
Medication use	Costs per 3 months	
Mesalazine	UC: 225.17[b]	(2)
	CD: 261.71[c]	(2)
Prednisone	16.00 [d]	(2)
Budesonide	201.20[e]	(2)
Azathioprine - 150 g/day	96.06[f]	(2)
Mercaptopurine - 50 mg/day	96.06[g]	(2)
Methotrexate - 15 mg/ week	263.35[h]	(2)
Infliximab	5,144.18[i]	(2)
	Unit price (€)	**References**
Adalimumab	4,625.84[j]	(2)
Surgery	Cost price per type of surgery [k]	
Ileocecal resection/ resection neoterminal ileum	1,255.04	(3)
Partial colectomy	1,829.00	(3)
Subtotal colectomy	1,829.00	(3)

	Unit price (€)	References
Adalimumab	4,625.84[j]	(2)
Surgery	Cost price per type of surgery [k]	
Ileocecal resection/ resection neoterminal ileum	1,255.04	(3)
Partial colectomy	1,829.00	(3)
Subtotal colectomy	1,829.00	(3)
Abcess surgery	178.08	(3)
Complex fistula surgery	2,440.12	(3)
Rectum amputation	3,337.94	(3)
Ileostomy	787.58	(3)
Diagnostic procedures	Cost price per type of diagnostic procedure	
Colonoscopy	364.42	(3)
CT scan	162.14	(3)
MRI scan	199.24	(3)
Abdominal X-ray	45.98	(3)
Ultrasonography	39.93	(3)
DXA scan	89.54	(3)
Laboratory	19.14[l]	(3)

[a] Price based on average cost price of 55 general practitioners (weekend/evening/night).

[b] Price based on average dose of 2000 mg/day during 91 days.

[c] Price based on average dose of 2400 mg/day during 91 days.

[d] Price based on average dose of 10 mg/day during 91 days.

[e] Price based on average dose of 6 g/day during 91 days.

[f] Price based on average dose of 150 mg/day during 91 days.

[g] Price based on average dose of 50 mg/day during 91 days.

[h] Price based on average dose of 15 mg/ week during 13 weeks.

[i] Price based on average weight of 75 kg and 1.8 infusions per 3 months.

[j] Price based on 6,5 injections per 3 months (81% administered adalimumab 40 mgs per 2 weeks) or 13 injections per 3 months (19% of patients administered adalimumab 80 mgs per 2 weeks).

[k] Days admitted at the surgical or medical were not included in the cost price of surgery, but assessed separately.

[l] Price based on full blood count and differential, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, y-glutamyl transferase, sodium, potassium, creatinine, albumin.

[m] For patients with an ileostomy costs for caring for the stoma were based on a standard care package. This is based on the assumption of an exchange of base disk 4 times per week and of the ileostomy bag twice/day.

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Supplementary Table 2. Results of the expert panel (input for the base case scenario)

Hospital nr	Expected growth of anti-TNF use over the years 2015-2019	Expected maximum price reduction of biosimilars relative to Remicade® price of the year 2014	Expected maximum price reduction of Remicade® relative to Remicade® price of the year 2014	Expected maximum price reduction of Humira® relative to Humira® price of the year 2014	Will these price reductions of anti-TNF occur immediately after the introduction of biosimilars or evolve gradually towards a maximum?	What price reduction relative to Remicade® price of the year 2014 is high enough to induce biosimilar therapy in anti- TNF naïve patients?	What price reduction relative to Remicade® price of the year 2014 is high enough to switch to biosimilars in patients who already use anti- TNF compounds?
1. a*	+5%	60%	50%	50%	Gradually	30%	50%
1. b*	+5%	60%	50%	50%	Gradually	20%	30%
2.	+5%	60%	50%	50%	Gradually	5%	25%
3.	+5%	60%	40%	40%	Gradually	5%	-
4.	+5%	70%	60%	60%	Gradually	50%	70%
5.	+10%	50%	50%	50%	Immediately	25%	25%
6.	+5%	60%	30%	15%	Gradually	10%	50%
7.a*	+10%	50%	30%	10%	Gradually	5%	- (or 70%)
7.b*	+5%	50%	60%	60%	Gradually	10%	60%
8.	+5%	20%	30%	30%	Gradually	25%	25%
9.	+5%	20%	50%	50%	Gradually	20%	20%
10.	+5%	40%	30%	30%	Gradually	25%	40%
11.	+10%	60%	60%	50%	Gradually	20%	30%
12.	+5%	50%	40%	30%	Gradually	30%	40%
13.	+10%	20%	40%	40%	Gradually	30%	50%

*These physicians work in the same hospital. Numbers in grey have not been taken into account in the base case scenario, because Remicade® and Humira® are not likely to become cheaper than biosimilars

Supplementary Table 3. Detailed results of the reference and base case scenario and estimated differences for the separate years and the sum of the simulated period

	2014	2015	2016	2017	2018	2019	In 5 years (total)
IBD-specific healthcare costs per CD patient in €							
Reference (mean)	5,950	5,960	5,970	5,980	5,990	6,000	29,900
Base case (mean (90%CI))	5,950 (5,950 –5,950)	5,710 (5,470 – 5.810)	5,010 (4,330 –5,680)	3,900 (3,050 –5.510)	2,990 (2,220 –5,230)	2,450 (1,870 –4,590)	20,040 (16,980 –26,800)
Difference (mean(90%CI))	-	-254 (-487 --153)	-966 (-1,640 - -294)	-2,080 (-2,930- -472)	-3,000 (-3,770 --762)	-3,550 (-4,130 --1,400)	-9,850 (-12,910 --3,140)
Median difference	-	-220	-1,180	-2,550	-3,540	-4,000	-11,400
IBD-specific healthcare costs per UC patient in €							
Reference (mean)	2,330	2,330	2,340	2,350	2,360	2,360	11,700
Base case (mean (90%CI))	2,330 (2,330 –2,330)	2,250 (2,200 –2,280)	2,100 (1,960 –2,240)	1,870 (1,700 –2,200)	1,690 (1,530 –2,140)	1,590 (1,470 –2,040)	9,500 (8,860 –10,900)
Difference (mean(90%CI))	-	-81 (-134 - -52)	-244 (-386 - -99)	-481 (-654 - -150)	-666 (-825 - -215)	-773 (-898 – -325)	-2,250 (-2,880 --859)
Median difference	-	-75	-287	-571	-773	-864	-2,550
IBD-specific healthcare costs per IBD patient in €							
Reference (mean)	3,960	3,970	3,970	3,980	3,990	4,000	19,900
Base case (mean (90%CI))	3,960 (3,960 –3,960)	3,810 (3,670 –3,870)	3,410 (3,020 –3,790)	2,780 (2,310 –3,690)	2,280 (1,840 –3,530)	1,980 (1,650 –3,190)	14,200 (12,500 –18,000)
Difference (mean(90%CI))	-	-159 (-293 - -98)	-569 (-952 - -187)	-1,200 (-1,680- -295)	-1,720 (-2,150 --461)	-2,020 (-2,350 --810)	-5,700 (-7,400 --1,890)
Median difference	-	-140	-690	-1,460	-2,020	-2,270	-6,550
Healthcare costs for the total Dutch IBD population (€ in millions)							
Reference (mean)	344	345	346	346	347	348	1,730
Base case (mean (90%CI))	344 (344 –344)	331 (320 – 337)	296 (263 – 330)	242 (200 – 321)	198 (160 – 307)	172 (143 – 277)	1,240 (1,100 –1,570)
Difference (mean(90%CI))	-	-14 (-25 - -8)	-49 (-83 - -16)	-105 (-146 - -26)	-149 (-187 - -40)	-176 (-205 - -70)	-493 (-643 - -164)
Median difference	-	-12	-60	-127	-175	-198	-570
Cost difference per 100,000 population1 (€ in millions)							
Difference (mean (90%CI))	-	-0.08 (-0.15 - -0.05)	-0.29 (-0.49 - -0.10)	-0.62 (-0.87 - -0.15)	-0.89 (-1.11 - -0.24)	-1.05 (-1.22 - -0.42)	-2.93 (-3.82 - -0.97)
Percentage of costs of anti-TNF/total healthcare costs in IBD patients							
Reference	61%	61%	61%	61%	61%	61%	
Base case (mean)	61% (61 – 61)	60% (59 – 61)	55% (50 – 60)	44% (34 – 59)	29% (17 – 57)	18% (7 – 52)	
Base case (median)	61%	61%	54%	40%	22%	11%	

"Reference" represent no introduction of biosimilars for anti-TNF therapy. Costs were rounded to three digits.

[1] Centraal Bureau voor de Statistiek. StatLine databank 2009 (http://statline.cbs.nl/StatWeb/default.aspx)

Supplementary Table 4. Total cost savings of sensitivity scenarios over five years (mean euros)

Alternative scenarios	**per CD patient (€)**	**per UC patient (€)**	**per IBD patient (€)**	**Dutch IBD population i (million €)**	**per 100.000 nhabitants2 (million €)**	**Percentage of costs of anti- TNF/ total healthcare costs in IBD patients in 2019 (mean, %)**
Low price reduction of anti- TNF compounds	946	310	596	52	0.31	59
High price reduction of anti-TNF compounds	13,000	2,910	7,440	647	3.84	5
Physicians switching to biosimilars on high price reductions	4,100	1,080	2,440	212	1.26	47
Physicians switching to biosimilars on small price reductions	12,300	2,750	7,060	614	3.65	10
Low percentage of anti-TNF switchers when the appropriate threshold is reached	4,920	1,250	2,900	252	1.50	44
High percentage of anti-TNF switchers when the appropriate threshold is reached	10,300	2,330	5,890	513	3.05	17
Maximum price reduction of biosimilars is immediately reached	11,400	2,560	6,500	568	3.38	16
New infliximab users all start with biosimilars	10,000	2,280	5,750	501	2.98	16
High market uptake of anti-TNF compounds	9,410	2,150	5,420	472	2.80	21
Remicade® and Humira® not reducing their prices	8,070	1,780	4,610	401	2.38	25

TNF: tumour necrosis factor. Costs were rounded to three digits.

[2] Centraal Bureau voor de Statistiek. StatLine databank 2009. (http://statline.cbs.nl/StatWeb/default.aspx)

CHAPTER 5.2

General discussion

5.2.1. INTRODUCTION

This thesis was aimed to provide insights in the past, current and future economic burden of inflammatory bowel disease (IBD), and the impact of smoking and non-adherence on IBD. This chapter is devoted to a general discussion of the results and the methods used. The most important findings are highlighted and their clinical relevance is discussed.

5.2.2. MAIN FINDINGS AND CLINICAL RELEVANCE

Chapter 2: Measuring the costs of IBD

Most of our studies were based on the COIN cohort. Cost data in the COIN study were based on patients' self-reported healthcare utilization. In **chapter 2.1**, we assessed the validity of self-reported healthcare utilization of IBD patients over the past year, and found that it correlated very well with medical records. We therefore felt confident that calculated costs in the COIN study (with a recall period of three months) represented true incurred healthcare costs of IBD patients in the Netherlands. Our results imply that, in future studies, data collection can be facilitated by simply asking patients about their consumed healthcare. In **chapter 2.2**, we studied the variation of healthcare costs of IBD patients over two years of follow-up (namely, from 2011 - 2013). Previously, our study group observed that healthcare costs of IBD patients had shifted from hospitalizations towards anti-TNF compounds by 2011.[1] In **chapter 2.2**, we concluded that from 2011 until 2013, total annual costs for IBD remained consistently high (namely €7,835 in CD and €3,600 in UC in 2013). We observed a further increase in the proportion of anti-TNF-related healthcare costs, which was offset by a decrease in hospitalization costs. These results undoubtedly reflect the current therapeutic approach in IBD with a more pronounced role for biologicals earlier in the course of disease.[2,3] Recent data on efficacy and safety of biologicals support this shift towards earlier implementation, which is aimed at averting progression early in the disease course before irreversible tissue damage has occurred.[4] The observed reduction in hospitalizations and possibly abdominal surgery is confirmed in other recently published data.[5] Our finding that the overall healthcare costs did not change, implies, from a financial perspective, that the shift to biologicals is compensated by less hospitalizations and other healthcare costs. Whether this is accompanied by an increased quality of life is presently not known.

Chapter 3: Impact of smoking on IBD

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.[6–10] In CD, smoking is associated with flares, hospitalizations, surgical procedures

and an increased use of immunosuppressive drugs, whereas in UC, smoking appears to be related to a reduced corticosteroid utilization and reduced risk of colectomy.[11–17] In this chapter, we analysed the impact of smoking on extra-intestinal manifestations (EIMs), IBD-related costs and health-related quality-of-life (HrQoL). Smoking was found to be common in IBD patients, with Dutch CD patients smoking more frequently than UC patients (21% versus 9%).

In **chapter 3.1**, the COIN study partnered with the Groningen study, focused on cigarette smoke exposure and disease behaviour in IBD, and the JOINT study, evaluating joint and back manifestations in IBD. In all three cohorts, the association between smoking and EIMs was explored. We found a higher prevalence of joint manifestations and chronic skin disorders in smoking CD and UC patients than in nonsmoking CD and UC patients. Moreover, we observed that smoking was significantly more common in CD and UC patients with joint manifestations. A dose-response relationship was suggested by the finding that EIMs appeared to be more prevalent in heavy smokers. Interestingly, EIM prevalence rapidly decreased to levels encountered in never-smokers when patients quit smoking. In **chapter 3.2**, we compared societal costs, work productivity and HrQoL between smokers, never-smokers and ex-smokers in the COIN study. We confirmed that smoking CD patients experienced a worse course of disease than did never-smokers (i.e. higher incidence of active disease and fistulas, increased risk of anti-TNF use). Ex-smoking UC patients more frequently experienced flares than did current smokers with UC. Annual societal costs were 31% higher in the smoking IBD population than in those who never smoked. Societal costs in IBD were mainly driven by healthcare costs, which were 40% higher in smokers than in never smokers, and 53% higher than in ex-smokers. Societal costs of IBD patients who quit smoking more than five years before inclusion were lower than those of patients who quit smoking within five years before inclusion. Moreover, smoking IBD patients suffered from greater impairment of work productivity and activity than did never-smokers. Also, the median HrQoL was lower in the smoking population than in never- and ex-smokers, which applied to both CD and UC. This chapter provides strong evidence for the substantial (negative) consequences of smoking in both CD and UC patients. Whether smoking has a true causal relationship with the deterioration of several components of the disease course cannot be deducted from our observational data.[18]

Smoking is one of the very few modifiable behavioural factors in IBD.[19] We therefore urge gastroenterologists to pursue an active approach towards smoking cessation in all (IBD) patients. Using the societal perspective, campaigns aimed at smoking cessation may result in considerably lower costs and less absenteeism. A recently published economic evaluation of a smoking cessation program for CD patients showed that all proposed strategies were cost-saving over a strategy with no program.[20] Gastroenterologists might be less inclined to encourage UC patients to stop smoking, due to concerns about flare-ups of the disease following smoking cessation.[21] Our finding that smoking UC patients have more EIMs, have a worse HrQoL, and have higher healthcare costs than non-smoking UC patients put

these concerns into perspective. With an intervention study, aimed at smoking cessation in both CD and UC patients, it would be possible to: a) observe direct effects of smoking cessation in CD and UC patients, b) study the pace of clinical disease alterations following smoking cessation (which is expected to be within two years based on our observational data), and c) measure cost savings prospectively.

Chapter 4: Burden of non-adherence on IBD

Medication adherence is crucial for successful treatment of a disease. Chronic diseases such as CD and UC are particularly susceptible to non-adherence, due to the fact that patients rely on maintenance therapy, aimed at preventing problems in the long run, often without discernible short-term benefits for patients. Medical therapy in IBD is aimed at maintaining remission, thereby preventing disease progression, complications, such as stricturing or penetrating disease and averting gastro-intestinal surgery.[22,23] Consequently, it can be assumed that non-adherence has detrimental effects on the disease course and associated healthcare costs.[24] In this chapter, we aimed to capture the burden of non-adherence in IBD. In **chapter 4.1**, we identified the optimal tool for measuring non-adherence for daily use in clinical practice. In **chapter 4.2**, our goal was to pinpoint patients at risk for developing non-adherent behaviour, and in **chapter 4.3**, we quantified the longitudinal consequences of non-adherence, in terms of disease flares, healthcare costs and HrQoL.

First, we assessed self-reported medication adherence in our study population using three tools: (1) the 8item Morisky Medication Adherence Scale (MMAS-8), (2) the single question how well patients take their daily medication using a visual analogue scale (VAS), and (3) the Forget Medicine scale (FM), assessing how often patients forget their medication (**chapter 4.1**). By means of a cross-sectional agreement among measures and a critical appraisal of the use of all tools, we found that these tools correlated well. The VAS was the easiest and quickest tool to assess adherence, while MMAS-8 provided insight in specific reasons for non-adherence. The main weakness of our study is the absence of a comparison with non selfreported measures.[25] Self-report is an easy and accessible method to assess medication adherence, but is less objective than biological assays or pharmacy refill data.[26,27] It is therefore possible that true nonadherence rates in the COIN study were higher than recorded. Non-adherence in the COIN study was recorded in 12.1% of CD patients and in 13.3% of UC patients (**chapter 4.2**), compared with 7% to 72%, respectively, reported in literature.[24] Non-adherence in our cohort was most frequently observed in patients using rectally administrated compounds, in patients on monotherapy and in patients having multiple administrations per day. During the 2.5 years of follow-up, patients recorded their medication adherence using a VAS every three months. We employed a generalized linear mixed model to identify patient- and disease- related factors predictive of non-adherence three months after the assessment of predictors. We found that lower age at diagnosis, a current flare, self-reported anxious or depressed feelings and current non-adherence

were independent predictors for future non-adherence in IBD. In addition, we found that adherence improved in a considerable number of non-adherent patients during follow-up, implying that adherence behaviour may be amendable. Interestingly, a higher perceived control of medical treatment and understanding of the disease was associated with high adherence to medical therapy. These findings corroborate the Common Sense Model, which states that patients' beliefs play an important role in the modification to the disease.[28,29] In **chapter 4.3**, we studied the longitudinal impact of adherence on healthcare costs, flares and HrQoL of CD and UC patients in the COIN cohort. Low adherence (defined as a VAS score <50%) in CD patients was associated with a 42% increase in total three-monthly healthcare costs after six months (+€255), explained by higher costs of medication use and hospitalization costs (these analyses were performed after extensive correction for significant covariates). Costs of low-adherent UC patients were higher but this did not reach statistical significance. Costs of UC patients are known to be three times lower than those of CD patients, which might explain why non-adherence did not translate into significantly higher costs in UC patients.[1] Low adherence was not clearly associated with the development of flares or a (temporary) decrease in HrQoL. Our findings regarding the increased healthcare costs of low-adherent patients in IBD are in line with literature,[25] but we were unable to show that non-adherence is associated with increased risk of flares.[30–32] Our follow-up period was probably too short to prove our hypothesis that low adherence first causes flares, which then results in increased healthcare costs (including increased costs for hospitalizations and medical therapy).

This chapter concluded that a VAS is the optimal tool for measuring adherence in clinical practice, that non-adherence can be predicted based on clinical parameters and that non-adherence causes a high economic burden to the healthcare system in IBD patients. After identifying non-adherence in patients, the first step in averting disease deterioration and rising costs would be to have the capability to improve adherence. Methods to improve adherence in IBD are presently being studied, but are beyond the scope of this thesis.[25,33] In general, multicomponent strategies (educational, cognitive or behavioural) are thought to be most effective in improving medication adherence.[34] If adherence would routinely be assessed in IBD patients, for example with a simple VAS, a decrease in adherence might be noticed in time. This might provide opportunities to discuss reasons for non-adherence. Since dealing with nonadherence will remain a challenge, future studies should focus on patient-tailored and multidimensional interventions.[25]

Chapter 5: Introduction of biosimilars

IBD is associated with a high economic burden to society. We identified anti-TNF compounds (infliximab and adalimumab) as the main cost drivers in IBD, accounting for 61% of annual IBD-specific healthcare costs (**chapter 2.2**). These biologic therapies have been introduced nearly 20 years ago,[35] and are perceived as the most effective agents available for the

medical treatment of IBD. In 2015, the Remicade® patent expired,[36] and infliximab biosimilars entered the market. A biosimilar is a copy version of licenced biological agents, which is brought to the market after patents of original agents expire. European Medicines Agency's (EMA) regulations ensure the quality, efficacy and safety of biosimilars in European countries. The main advantage of the introduction of biosimilars is that increased competition can be expected to lead to decreased costs and increased availability of biological therapy.

In **chapter 5.1**, we build a model to simulate the impact of the introduction of biosimilars on IBD-related healthcare costs in the Netherlands for the years 2015 to 2019. We made assumptions, which were critically appraised by an expert panel of fifteen gastroenterologists with expertise in the field of IBD, on possible price reductions of anti-TNF compounds, anti-TNF prescription rates and development of hospitalization costs. In the base case scenario, we assumed a gradual decrease in prices of biosimilars up to 60%, a gradual decrease in prices of original anti-TNF compounds up to 50%, and an annual increase of the anti-TNF prescription rate of one percent. In this scenario, total cost savings for the Dutch healthcare system approximated €500 million within five years after the introduction of biosimilars. Sensitivity analyses revealed that results were predominantly determined by factual price reduction of anti-TNF therapy, threshold price reduction at which physicians are willing to switch patients towards biosimilars and the extent to which switching takes place. Even when an increase in prescription rate of biologicals was modelled (triggered by lower unit prices), large cost savings were concluded. Large cost savings have been observed after the introduction of other biosimilars previously[37] and budget impact studies performed in other countries confirm that the introduction of biosimilars for infliximab will result in considerable savings for the Dutch healthcare system.[38-40]

However, there are concerns for inferior clinical outcomes, the safety profile and the risk of increased immunogenicity due to development of antidrug antibodies after switching from originator to biosimilar. Studies on the perception of gastroenterologists of biosimilars revealed a high degree of scepticism regarding these potential drawbacks. In a survey of 307 IBD specialists, 64% disagreed with automatic replacement of original biologicals with a biosimilar, 18% supported substitution for new prescriptions and only 6% felt that biosimilars were interchangeable.[41] Most IBD specialists were not confident about the use of biosimilars in clinical practice. The perspective of the IBD patient was assessed in a large online survey.[42] The participants worried about biosimilars' safety (47.0%) and efficacy (40.3%). Only 25.2% of the respondents had no concerns about biosimilars. More than half of the participants thought that the lower costs of biosimilars should not come before their safety and efficacy. Over the last two years, the evidence for the efficacy and safety of biosimilars in CD and UC, both for anti-TNF naïve patients and patients in whom originators are switched towards biosimilars has accumulated.[43,44] Consequently, the scepticism of gastroenterologists is rapidly decreasing.[45] Moreover, the advent of several infliximab and adalimumab biosimilars in the next few years can be expected to provoke

further price reductions.[46] This will lower the bar for the use of biosimilars in an increasing number of IBD patients.

5.2.3. METHODOLOGICAL CONSIDERATIONS

Study design

The COIN study was observational in design, mainly for feasibility reasons. This enabled quantifying of costs and HrQoL in a large, representative Dutch cohort. Data collection was performed prospectively, in order to minimize recall bias,[47,48] to detect in-person changes over time regarding the course of disease, healthcare utilization, HrQoL and medication adherence, and to identify patients at risk for certain outcomes during follow-up (for example for increased costs or for developing non-adherence)(**chapter 2.2** and **chapter 4.2**).

Patient recruitment

The study domain comprised adult IBD patients from seven university medical centres and seven general hospitals. The aim was to recruit a group of patients, representative for the whole Dutch adult IBD population (which was estimated at 85,400 in 2012).[49] Patients were identified using the diagnosis treatment combinations (DTCs) for respectively CD and UC.[50,51] In total, 9,550 IBD patients were invited by letter to participate, of whom 3,030 IBD patients responded (response rate 32%). Possibly, a subtype of patients is generally more willing to participate in longitudinal studies, which may have introduced sampling bias.[52] To assess whether included IBD patients were representative for the study domain, a non-responder analysis was performed.[1] There were no relevant statistical significant differences regarding demographic data and disease course items between these groups. A certain degree of sampling bias could not be excluded since IBD patients treated by general practitioners were not included in the COIN cohort. Nonetheless, in the Netherlands, most patients with an established diagnosis of IBD are treated in hospitals. The web-based method of data collection did not noticeably lead to an underrepresentation of elderly IBD patients, with the inclusion of 302 (10%) patients, older than 65 years of age. This can be explained by the very high internet penetration of 89% in the Netherlands in 2012.[53]

Ethical considerations

The COIN study was centrally approved by an ethics committee. Patient data were stored in a database in which only patient codes were visible. The researchers did not have access to the electronic patient record of patients. Therefore, no extensive monitoring of the study was required, which normally can lead to high study costs. However, we were not able to

externally validate findings through access to patient records, and we were not able to collect extra data of patients when required.

Data collection

All data were assessed by self-report. In **chapter 2.1**, we assessed the validity of self-reported healthcare utilization of IBD patients over the past year, and found that it correlated very well with medical records. For some of the study parameters, self-report may not be an optimal method. For example, some patients reported to have UC *and* to suffer from fistulas. In clinical practice, physicians would switch the diagnosis from UC to CD in most of these patients. Therefore, in order to avoid contamination of the UC and CD phenotypes, we labelled this category of patients as 'IBD-unknown'. Reassuringly, we were able to confirm previously reported disease outcome data, supporting the internal validity of the COIN study.[1]

After baseline, follow-up questionnaires were sent at intervals of three months. This enabled us to calculate three-monthly costs per patient. For our cost analyses, we chose to include both healthcare costs (such as medication costs), patient costs (such as travel costs) and productivity losses due to IBD illness.[54] Productivity losses were calculated using the human capital approach.[55] Costs were analysed from a healthcare perspective, and in some studies from a societal perspective. The inclusion of patient costs and work-productivity losses in addition to healthcare costs is generally encouraged.[54] Though, many cost-of-illness studies are still limited to healthcare costs. We did not include indirect healthcare costs in our analysis (i.e. costs attributed to life years gained due to treatment). The inclusion of indirect healthcare costs may not be relevant for IBD since IBD is not associated with premature death (with studies reporting lower mortality rates,[56] equal mortality rates,[57–59] and increased mortality rates[56,57,60] in IBD compared with the general population).

To ensure the validity of the results and to reduce measurement bias, a consistent manner of data collection is required.[61] In the COIN study, validated questionnaires such as the IBDQ[62] and the short Crohn's Disease Activity Index[63] were therefore assessed every three months in an uniform way. As a result, some of the specific questions were asked repetitively in the questionnaire. In the free comment section at the end of the questionnaire, many patients complained about this issue, and some even decided to discontinue their participation in the study for this reason. During follow-up, we added a few extra components to the questionnaire. For example, on one occasion (at 2.5 years) the validated Modified Morisky Adherence Scale[64,65] was incorporated to validate the medication adherence assessment tool in the COIN study (**chapter 4.1**). Adding components at single time-points during a prospective cohort study allows researchers to assess cross-sectional associations that were not previously studied.

(Loss to) follow-up

During 2.5 years of follow-up, an increasing number of patients was lost to follow-up. After 2.5 years, 934 of 3,030 initial patients were still in study. Reasons for drop-out included death of patients, the inability to reach patients due to automatic email response bouncing our request (possibly due to a change of email address), withdrawal of consent and unknown reasons. Withdrawal of consent was mostly due to complaints about the length of the questionnaires, and the relatively high perceived frequency of the questionnaires being sent. Regarding the latter, the vast majority of healthcare costs could also be calculated from self-reported healthcare consumption once a year, since hospitalizations, surgical procedures and anti-TNF use, accounting for 86.2% of total healthcare costs in CD and 60.6% in UC,[1] were well remembered by patients (**chapter 2.1**). However, detailed information on hospital visits, diagnostic procedures, but also HrQoL and absenteeism due to illness might be under- or overreported when the recall time increases. It remains a challenge to find the right balance between retaining most participants during follow-up, and collecting reliable patient-related data as much as possible.

A systematic review aimed to assess retention strategies for in-person follow-up in healthcare studies was recently performed.[67] Their main recommendation was that studies should use many different strategies in order to retain as much as possible participants. Proposed strategies specific for postal or electronic questionnaires included regular reminders, shorter questionnaires, personalized questionnaires, nonmonetary incentives and offering survey results to participants.[68] In the COIN study, we send regular newsfeeds to participants, including latest study results.

In general, loss to follow-up is of major concern in prospective cohort studies. When drop-out of patients is not random, it can lead to (attrition) bias.[18] In the COIN study, full responders after two years of follow-up were older and had longer disease duration compared with non-responders (**chapter 2.2**). It is therefore plausible that (a part of) loss to follow-up was not coincidental. In the analyses of outcomes collected during follow-up, it was therefore mandatory to account for missing follow-up data by using generalized mixed models (**chapter 2.2**) and multiple imputation techniques (**chapter 4.2** and **chapter 4.3**). One study[66] revealed that in general, younger patients, patients with a lower education, and current smokers are more likely to be lost to follow-up in prospective cohort studies.

Dealing with confounding

Confounding frequently occurs in observational studies.[18] With the COIN study, we explored the association between smoking and healthcare costs (**chapter 3.2**). Smoking was found to be associated with high healthcare costs and low HrQoL in IBD patients. We aimed to correct for confounding in the analysis stage. However, in observational studies, it

is unlikely that all potential confounders are measured and adjusted for. Therefore, residual confounding can never be excluded in these types of studies.

Conclusion – methodological considerations

The COIN study was designed to study the costs and HrQoL of IBD patients in the Netherlands. The large study population at baseline and the detailed prospective study design allowed for many new associations to be found. Longitudinal studies are often complicated by a variety of confounders and have to deal with a significant loss of participants. These issues should be addressed in the analysis of the data.

5.2.4. Final remarks

This thesis described several economic and societal aspects of IBD. Our main findings were:

- Self-reported healthcare utilization of inflammatory bowel disease patients correlates well with medical records
- The proportion of anti-TNF-related healthcare costs in IBD is still increasing, which is offset by a further decrease in hospitalization costs
- Smoking is associated with extra-intestinal manifestations, higher disease-related costs and lower quality-of-life in IBD
- A visual analogue scale seems the most appropriate tool for quantifying medication adherence in clinical IBD practice
- Lower are at diagnosis age, flares, feelings of anxiety or depression, and current non-adherence are associated with future non-adherence in patients with IBD
- Medication non-adherence is associated with increased healthcare costs in CD patients
- The introduction of biosimilars in IBD is likely to result in large healthcare savings.

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Summary in Dutch (Nederlandse samenvatting)

HOOFDSTUK 1: INTRODUCTIE

Inflammatoire darmziekten ('Inflammatory Bowel Disease' of "IBD"), waartoe de ziekte van Crohn ('CD') en colitis ulcerosa ('UC') gerekend worden, zijn chronische ontstekingsziekten van het maagdarmkanaal. De oorzaak van IBD is nog niet volledig bekend, maar er wordt gedacht dat zowel genetische- als omgevingsfactoren een rol spelen. Naar schatting lijden meer dan 1 miljoen inwoners van de Verenigde Staten, en meer dan 2.5 miljoen Europeanen, momenteel aan IBD. Het natuurlijk beloop van IBD bestaat uit opvlammingen maar ook uit (langdurige) remissies. Daarnaast kunnen IBD patiënten lijden aan zogenaamde 'extra-intestinale manifestaties' (EIMs) van de ziekte, waarbij onder meer de gewrichten, de huid of de ogen kunnen zijn aangedaan. Vanwege het chronische aspect heeft IBD substantiële invloed op het sociaal-maatschappelijk functioneren van patiënten. Zo heeft IBD een negatieve invloed op de arbeidsproductiviteit en de kwaliteit van leven van patiënten. Vanuit een maatschappelijk perspectief brengt IBD aanzienlijke kosten met zich mee, welke bestaan uit zowel gezondheidszorgkosten (zoals medicatiekosten), kosten voor de patiënt (zoals reiskosten naar het ziekenhuis) en kosten ten gevolge van werkverzuim door IBD. In dit proefschrift hebben wij ons gericht op de maatschappelijke en economische aspecten van IBD. De belangrijkste resultaten in deze samenvatting delen we op in de volgende hoofdstukken: (2) Meten van de kosten van IBD, (3) Impact van roken op IBD, (4) Impact van non-adherence op IBD en (5) Introductie van biosimilars in IBD.

HOOFDSTUK 2: METEN VAN DE KOSTEN VAN IBD

Onze studieresultaten zijn voor een belangrijk deel gebaseerd op het COIN cohort ("Costs of Inflammatory Bowel Diseases in the Netherlands"). De COIN studie is een prospectieve cohortstudie naar de kosten van IBD in Nederland. In deze studie werden data gegenereerd door patiënten zelf. In **hoofdstuk 2.1** hebben we onderzocht of zelf-gerapporteerde gezondheidszorgkosten overeenkomen met kosten, gebaseerd op de in de medische status van patiënten genoteerde behandelingen en diagnostiek. De correlatie tussen zelf-rapportage en de medische status was erg hoog, waaruit wij concludeerden dat de kosten data uit de COIN studie goed bruikbaar zijn om de kosten van IBD in Nederland te meten. In **hoofdstuk 2.2** laten we zien dat momenteel anti-TNF therapie het grootste deel van de totale IBD-gerelateerde kosten voor de maatschappij bepaalt. Daarentegen zijn de kosten voor ziekenhuisopnames aanzienlijk afgenomen gedurende de afgelopen jaren, wat mogelijk een gevolg is van deze anti-TNF therapie. Netto gezien zijn de totale maatschappelijke uitgaven voor IBD over de afgelopen jaren stabiel gebleven in Nederland. Dit suggereert dat de stijging van de anti-TNF gerelateerde kosten wordt gecompenseerd door een daling van kosten door ziekenhuisopnames. De maatschappelijke kosten per patiënt per jaar waren €7,835 in het geval van CD en €3,600 in het geval van UC in 2013.

HOOFDSTUK 3: IMPACT VAN ROKEN OP IBD

Roken is een bekende omgevingsfactor van invloed op IBD. Roken lijkt slecht te zijn voor patiënten met CD, maar juist gunstige effecten te hebben bij UC patiënten. In dit hoofdstuk hebben we onderzoek gedaan naar de effecten van roken op EIMs, IBD-gerelateerde maatschappelijke kosten en de kwaliteit van leven gerelateerd aan IBD. In onze studiepopulatie (het COIN cohort) rookte 21% van de CD patiënten en 9% van de UC patiënten. In **hoofdstuk 3.1** hebben we een samenwerkingsverband opgezet met twee andere cohorten om de impact van roken op EIMs te onderzoeken: het Groningencohort, hetgeen opgezet is om de effecten van roken op IBD te onderzoeken, en het JOINT cohort, hetgeen gewrichts- en rugklachten bij IBD patiënten bestudeert. In alle drie de cohorten vonden we een sterke associatie tussen roken en EIMs: EIMs kwamen vaker voor bij rokers, en andersom rookten patiënten met gewrichts- en huidmanifestaties van IBD vaker. We observeerden daarnaast een dosis-respons relatie aangezien zware rokers vaker EIMs hadden dan lichte rokers, en zagen dat de prevalentie van EIMs daalde na het stoppen met roken. In **hoofdstuk 3.2** hebben we de maatschappelijke kosten en de kwaliteit van leven vergeleken tussen rokende -, ex-rokende en nooit gerookt hebbende IBD patiënten in de COIN studie. We konden bevestigen dat rokende CD patiënten een heftiger ziektebeloop hadden dan niet-rokende CD patiënten, en dat ex-rokende UC patiënten vaker opvlammingen van de ziekte hadden dan huidige rokers met UC. Rokende CD patiënten hadden dan ook hogere maatschappelijke kosten dan niet rokers, en ondanks dat rokende UC patiënten een milder ziektebeloop hadden dan ex-rokers, hadden zij geen lagere kosten vergeleken met niet-rokers. Rokende IBD (CD+UC) patiënten hadden 31% hogere maatschappelijke kosten dan IBD patiënten die nooit hadden gerookt. Totale gezondheidszorgkosten van huidige rokers waren 40% hoger dan van nooit-rokers en 53% hoger dan van ex-rokers. De maatschappelijke kosten van ex-rokers die meer dan vijf jaar geleden waren gestopt met roken waren significant lager dan de maatschappelijke kosten van ex-rokers die minder dan vijf jaar geleden waren gestopt. Dit hoofdstuk heeft kortom nieuwe aanwijzingen geleverd voor de sterke negatieve relatie tussen roken en EIMs bij zowel CD als UC patiënten.

HOOFDSTUK 4: IMPACT VAN NON-ADHERENCE OP IBD

De effectiviteit van behandeling van ziektes is afhankelijk van therapietrouw. In de internationale literatuur worden verschillende termen gebruikt voor therapietrouw. De term 'adherence' wordt hierbij het vaakst gehanteerd. Adherence geeft de mate aan waarin de afspraken tussen de patiënt en zorgverlener worden nageleefd. Non-adherence komt regelmatig voor bij chronische ziekten, niet in de laatste plaats omdat de patiënt het positieve effect van onderhoudstherapie op de korte termijn niet opmerkt. Het doel van medicatie bij IBD is het voorkomen van complicaties van de ziekte. De hypothese is dan ook dat non-adherence schadelijke effecten heeft op het ziektebeloop van IBD, en

uiteindelijk tot hogere ziektekosten leidt. Het doel van **hoofdstuk 4.1** was om de optimale methode te identificeren om non-adherence te meten in de dagelijkse praktijk. In **hoofdstuk 4.2** probeerden we te identificeren welke IBD patiënten een verhoogd risico hebben om in de toekomst non-adherent te worden, en in **hoofdstuk 4.3** hebben we de effecten op middellange termijn van non-adherence in kaart gebracht (het ontstaan van opvlammingen, gezondheidszorgkosten en de kwaliteit van leven).

Zelf-gerapporteerde medicatie adherence bij IBD patiënten uit het COIN cohort werd gemeten met drie verschillende methoden: (1) de 8-item 'Morisky Medication Adherence Scale' (MMAS-8); (2) de vraag hoe goed patiënten hun dagelijkse medicatie innamen met een zogenaamde 'Visual Analogue Scale '(VAS); en (3) de ' Forget Medicine Scale', waarmee gemeten kon worden hoe vaak patiënten hun medicatie vergaten Alledrie de methoden bleken goed met elkaar te correleren. Omdat de VAS een eenvoudige en snelle methode is, voldoet deze goed als instrument om medicatie adherence in de praktijk te meten. De MMAS-8 kan worden ingezet om redenen voor non-adherence te identificeren. In **hoofdstuk 4.2** vonden we non-adherence (VAS <80%) in 12.1% van de CD patiënten en in 13.3% van de UC patiënten. Non-adherence kwam het meest voor bij patiënten die rectaal toegediende medicatie voorgeschreven kregen, bij patiënten die behandeld werden met maar één medicament en bij patiënten die meer medicatie toedieningen per dag hadden. Tijdens tweeëneenhalf jaar follow-up hebben we elke drie maanden medicatie adherence door middel van de VAS geregistreerd van de COIN deelnemers. We vonden dat een lagere leeftijd bij IBD diagnose, een ziekteopvlamming, gevoelens van angst of depressie en actuele non-adherence voorspellende factoren waren voor toekomstige non-adherence (gedefinieerd als non-adherence drie maanden na het meten van de voorspellers). Opvallend was dat een significant deel van de non-adherente patiënten op een bepaald moment aangaf zijn of haar medicatie adherence te verbeteren tijdens de daarop volgende drie maanden. Dit suggereert dat adherence gedrag te modificeren is, althans bij patiënten met IBD. Een sterker gevoel van controle over de behandeling, en een beter begrip van de ziekte waren geassocieerd met een betere adherence. In **hoofdstuk 4.3** vonden we dat een lage adherence (VAS <50%) bij CD patiënten geassocieerd was met een 42% toename (+€255) van de totale driemaandelijkse gezondheidszorgkosten na zes maanden tijd. Deze toename van kosten bestond zowel uit hogere medicatie kosten als hogere kosten voor ziekenhuisopnames, gecorrigeerd voor revelante covariabelen. Bij UC waren de gezondheidszorgkosten van patiënten met een lage medicatie adherence ook hoger, maar de verschillen tussen laag- en hoog adherente patiënten was niet statistisch significant. Lage adherence was niet geassocieerd met de ontwikkeling van opvlammingen of een verslechtering van de kwaliteit van leven. De belangrijkste bevindingen van dit hoofdstuk zijn dat een VAS een eenvoudige en praktische manier is om medicatie adherence in de klinische praktijk te meten, dat non-adherence voorspeld kan worden door middel van een aantal klinische parameters en dat non-adherence bij patiënten met CD, en in mindere mate bij patiënten met UC, leidt tot een stijging van de gezondheidszorgkosten.

HOOFDSTUK 5: INTRODUCTIE VAN BIOSIMILARS

IBD gaat gepaard met hoge maatschappelijke kosten, die tegenwoordig voornamelijk worden veroorzaakt door dure geneesmiddelen, 'biologicals', zoals anti-TNF therapie (infliximab, adalimumab). In 2015 verliep het patent voor Remicade® (infliximab), waarna kopieën van deze middelen, biosimilars, op de markt kwamen. Biosimilars zijn vaak goedkoper dan hun origineel, en kunnen marktcompetitie veroorzaken. In **hoofdstuk 5.1** hebben we een model gebouwd om de impact van de introductie van biosimilars voor Remicade op de gezondheidszorgkosten in Nederland te simuleren. We hebben aannames gedaan die we baseerden op een expertpanel van vijftien IBD-artsen. In ons basisscenario namen wij aan dat biosimilars uiteindelijk 60% goedkoper zouden worden vergeleken met originele therapie, dat originele anti-TNF therapie 50% in prijs zou dalen en dat er een toename van één procent per jaar was in het aantal IBD patiënten bij wie anti-TNF therapie wordt voorgeschreven. Op basis van dit scenario werd er een totale kostenbesparing voor de Nederlandse gezondheidszorg berekend van €493 miljoen gedurende de eerste vijf jaar na de introductie van biosimilars. Sensitiviteitsanalyses toonden dat de uiteindelijke kostenbesparing voornamelijk bepaald werd door zowel de daadwerkelijke prijsdaling van anti-TNF therapie als ook de bereidheid van de arts om een patiënt een biosimilar in plaats van een origineel middel voor te schrijven. In de komende jaren worden er meer biosimilars op de markt verwacht, waardoor de kosten van het gebruik van anti-TNF-middelen bij patiënten met IBD wellicht nog verder zal dalen dan we nu gemodelleerd hebben.

BELANGRIJKSTE CONCLUSIES VAN DIT PROEFSCHRIFT:

- Gezondheidszorgkosten gemeten met zelf-rapportage correleren erg goed met kosten die geregistreerd zijn in de medische status van IBD patiënten
- De maatschappelijke kosten van IBD bestaan in toenemende mate uit anti-TNF gerelateerde kosten; hier tegenover staat een daling van de kosten door ziekenhuis opnames
- Roken is geassocieerd met extra-intestinale manifestaties, hogere IBD-gerelateerde maatschappelijke kosten en een slechtere kwaliteit van leven bij IBD patiënten
- Een 'visual analogue scale' lijkt de meest eenvoudige en effectieve methode om medicatie adherence in de praktijk te meten bij IBD patiënten
- Een lagere leeftijd bij IBD diagnose, angst of depressie en actuele non-adherence zijn voorspellend voor toekomstige non-adherence bij IBD patiënten
- Medicatie non-adherence is geassocieerd met hogere gezondheidszorgkosten bij CD patiënten
- De introductie van biosimilars bij IBD gaat gepaard met forse dalingen van de gezondheidszorgkosten van IBD.

Curriculum Vitae

Mirjam Severs was born on the 16th of July 1988 in Eindhoven. After graduation from secondary school in 2006, she started studying Nutrition and Health at the University of Wageningen. In 2007, she started Medical School at the University of Utrecht. During her graduation year, she performed a research internship on the predictive performance of faecal calprotectin on flares in inflammatory bowel disease patients at the department of Gastroenterology and Hepatology of the University Medical Centre Utrecht (UMCU), supervised by dr. B. Oldenburg. This project was awarded Best Student Abstract during the annual meeting of the Dutch society of Gastroenterology in 2013. In February 2014, Mirjam received her medical degree and started working on her PhD project at the department of Gastroenterology and Hepatology of the UMCU under guidance of Prof dr. P.D. Siersema, dr. B. Oldenburg and dr. M-J.J. Mangen. While finishing her PhD project, she started her residency in Internal Medicine of the UMCU in May 2016 as the first part of her residency program of Gastroenterology and Hepatology.

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Student Award Best Abstract, Dutch society of Gastroenterology, Veldhoven, 2013

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is maar goed ook want binnenkort word ik jouw achterbuurvouw! **Max**, statistiek bedrijven deed jij met twee vingers in de neus. Je kwam voornamelijk op werk om de dagelijkse lijst YouTube filmpjes bij te werken, iedereen van koffie te voorzien en om in de Brink te eten zodat je zelf niet hoefde te koken. Nadat jij vertrok als onderzoeker ben je nog lang blijven hangen bij de MDL borrels. Gelukkig, want je wordt gemist. **Daisy**, in een ver verleden was ik jouw coassistente toen jij als semi-arts op de MDL afdeling floreerde. Wat grappig om jou later als collega tegen te komen! **Vincent**, als ik aan jou denk, zie ik een jonglerende jongeman die enkel 'Yes yes girl' verkondigt. Maar onder dat laagje humor ligt een integere, slimme en erg collegiale collega.. **Tim**, ik vind het knap hoe jij je hockey carrière met je ziekenhuiswerk heb weten te combineren. En ook nog altijd van de partij bij borrels. Welke rol je dan ook aanneemt, je bent overal dezelfde, eerlijke en welbespraakte Tim. **Faydra**, als internist in spé heb jij maar mooi je mannetje weten te staan tussen alle MDLers. Zonder te klagen heb jij bergen werk verzet in korte tijd, en binnenkort ga ook jij al weer promoveren. Ik vind het bewonderingswaardig dat jij voor je principes opkomt, blijf dat de komende jaren vooral doen! **Wouter**, 'professor chaos', waar jij bent is drukte. Je had een vrij beroerd gevoel voor timing aangezien je soms op het vliegveld pas bedacht om je studies aan me over te dragen tijdens jouw vakanties. Met jouw uitzonderlijke scherpe humor maak je me echter tekens weer aan het lachen. Meer structuur is in aantocht nu Sjerrif op tijd z'n loopje moet doen en er gezinsuitbreiding aan zit te komen. Ik vind het knap hoe je alle ballen omhoog weet te houden! **Femke**, je bent maar kort bij ons geweest, maar jij en je zus hebben wel even duidelijk gemaakt dat je van een Amelung veel kunt verwachten. Het was erg gezellig om samen naar San Diego te gaan. **Joren**, ik heb met alle vertrouwen de Surveillance studie aan je overgedragen. Je bent een enorm betrouwbare collega met een goede dosis humor die je gelukkig steeds vaker laat zien. **Yara** (voor mij blijf je Bakkes), jij streek vanuit het Amsterdamse bij ons neer om even de lat een kilometer hoger te leggen. Je bent bereid om hard te werken en hebt in korte tijd een prachtig netwerk opgezet. Gelukkig wissel jij werk ook af met de leuke dingen van het leven zoals sporten, vrienden en mooie vakanties! Zit je ook wel eens op de bank? **Eelco**, je bent met een ambitieus project begonnen maar ik weet zeker dat het een succes gaat worden. Niet veel mensen doen het je na, twee masters en een PhD traject. Men keek uit naar de komst van 'de nieuwe Max.' Gelukkig weet jij volgens mij jij je grenzen prima te bewaken. **Anouk**, we hebben het leuk gehad in Washington toen jij als student daar al een praatje had weten te scoren. Dat belooft wat, heel veel succes met de nieuwe projecten!

Mijn familie wil ik hier graag noemen. Ondanks onze 'expansiedrift', welke er toe leidt dat er altijd iemand van ons de hort op is, zijn wij moeiteloos in alles wat wij doen verbonden. Ik vind dat bijzonder. **Papa**, ik kan veel leren van jouw ervaringen als inmiddels bijna gepensioneerd arts. In ons doen lijken wij enorm op elkaar, en je herkent dan ook mijn keuzes als die van jou. Jij helpt me relativeren. Soms gaat dat relativeren zo ver dat er niks meer over blijft van alles waar we mee bezig zijn. En dan wordt het soms eindelijk even

rustig in mijn hoofd. **Mama**, jij probeert altijd mijn creatieve kant te stimuleren. Je hebt enorme talenten maar je blijft onterecht bescheiden. Wat ben ik blij met jouw mooie kaft! Ik hoop dat na het afronden van mijn promotietraject dat ik weer eens bij jou in de leer mag. Je heb een haarfijne intuïtie waarmee je me vaak helpt. **Rosanne**, hoe jij je eigen bedrijf hebt opgezet, hoe jij talen je moeiteloos eigen maakt, hoe jij zo de wereld intrekt en grote netwerken opbouwt is bewonderenswaardig. Problemen die je onderweg tegen komt, los je zelf op. Het lijkt voor de buitenwereld alsof jij van hoogtepunt naar hoogtepunt hopt, maar ik weet hoe hard jij hier voor werkt. Met de komst van Leila en Noor is bij jou inmiddels de rust gelukkig wat teruggekeerd. Tegenwoordig ben jij degene die voor rust, reinheid en regelmaat pleit. Wie weet neem ik nog eens dat advies van je aan. Lieve familie, aan onze eettafel blijft niks onuitgesproken en oordelen, gedachten en gevoelens worden ongevraagd op tafel gelegd. Een dag geen discussie gevoerd is een dag niet geleefd. **Steven, Sharon en Ruud**, ik ben dan ook blij dat jullie alle drie de ontgroening van de familie Severs hebben doorstaan. Mijn schoonfamilie **Con, Marja, Yvonne en Ben,** ik was meteen welkom bij jullie. Het geeft een fijn gevoel dat jullie deur altijd wagenwijd open staat. Andersom geldt dat precies hetzelfde!

Lieve **vrienden en vriendinnen**, dank jullie wel voor de afleiding van werk. Wat is het leven zonder vrienden!

Lieve Ruud, ondanks dat wij een compleet andere familie, een andere carrière, vrienden en hobby's hebben, delen wij al meer dan 10 jaar de blik op de wereld om ons heen. Met jou naast me heb ik nooit het gevoel dat ik ergens alleen voor sta. Onze kracht is dat we elkaar de wereld gunnen. Ik kijk met vol vertrouwen uit naar alles wat ons samen nog te wachten staat.