Crohn's disease and ulcerative colitis

Occurrence, course and prognosis during the first year of disease in a European population-based inception cohort

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PREFACE

The present thesis is based on the following manuscripts:

I. Burisch J, Cukovic-Cavka S, Kaimakliotis I, et al. Construction and validation of a web-based epidemiological database for inflammatory bowel diseases in Europe - An EpiCom study. J Crohns Colitis. 2011 Aug;5(4):342-9.
II. Burisch J, Pedersen N, Cukovic-Cavka S, et al. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. Gut. 2013 Apr 20. In press
III. Burisch J, Pedersen N, Cukovic-Cavka S, et al. Initial disease course and treatment in an inflammatory bowel disease inception cohort in Europe – The ECCO-EpiCom cohort. Inflamm Bowel Dis 2013. In press
IV. Burisch J, Weimers P, Pedersen N, et al. Quality of life improves during one year of medical and surgical treatment in a European population-based inception cohort of patients with inflammatory bowel disease – An ECCO-EpiCom study. (Submitted)
V. Burisch J, Pedersen N, Cukovic-Cavka S, et al. Environmental factors in a population-based inception cohort of inflammatory bowel disease patients in Europe – An ECCO-EpiCom study. J Crohns Colitis. In press
VI. Burisch J, Vardi H, Pedersen N, et al. Resource utilization and costs in an inflammatory bowel disease inception cohort differs between Western and Eastern European countries – An ECCO-EpiCom study. (Submitted)
VII. Burisch J, Vegh S, Pedersen N, et al. Is there a difference in Quality of Care in a European inflammatory bowel disease inception cohort? – An ECCO-EpiCom study. (Submitted)

1. INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), are chronic immune-mediated diseases of the gastrointestinal tract. The aetiology of IBD remains unknown, but the diseases are thought to be caused by a complex interaction of genetic[1] and environmental factors[2] – including dietary components and tobacco – resulting in an inappropriate activation of the mucosal immune system driven by a loss of tolerance towards gut commensal bacteria[3]. The diagnosis of IBD is based on clinical, endoscopic, radiological, and histological findings according to various diagnostic criteria[4–6].

Both CD and UC are characterized by a chronic disease course with periods of remission and of active intestinal inflammation (diarrhoea, abdominal pain, bloody diarrhoea, as well as pus and mucus per rectum) that may require hospitalization[7,8]. Treatment of IBD consists of anti-inflammatory and immunosuppressive drugs including biological therapy with TNF-α inhibitors for inducing and maintaining remission, and surgery if there is a lack of response to medical treatment[9,10]. Due to their chronicity and unpredictable disease course, a mostly young age of onset, and the need for expensive medical and surgical therapies, IBD represents an important public health problem affecting the patients' education, working abilities, and health-related quality of life (HRQoL).

Traditionally, IBD is more common in industrialized than in non-industrialized countries, with the highest incidence rates reported in Scandinavia[11–15], the United Kingdom[16,17], and North America[18,19]. In Europe alone more than three million people are estimated to be affected by IBD[20]. However, the classic geographical distribution of the disease is changing as traditionally low-incident regions such as Eastern Europe[21,22] have recently reported rising incidence rates that mean their IBD occurrence is comparable to Western Europe. The reasons for this rising incidence are uncertain. An increase in disease awareness, improved access to healthcare and diagnostic procedures, or true changes in lifestyle and environmental factors as a consequence of the socioeconomic transition from 'developing' to 'developed' in many Eastern European countries could all account for some of the changes[23,24]. However, data on the epidemiology of IBD in Eastern Europe, including disease course and treatment choices, are limited both by the small number of studies available and by most studies being retrospective or referral centre-based, and very few originating from population-based studies[25,26]. The occurrence of IBD in Eastern Europe could simply have been underestimated. It is therefore of interest to follow the evolving trends of IBD occurrence in order to describe real differences among geographical regions across Europe.

Population-based inception cohorts, including incident (newly diagnosed) patients, offer the most valid picture when studying

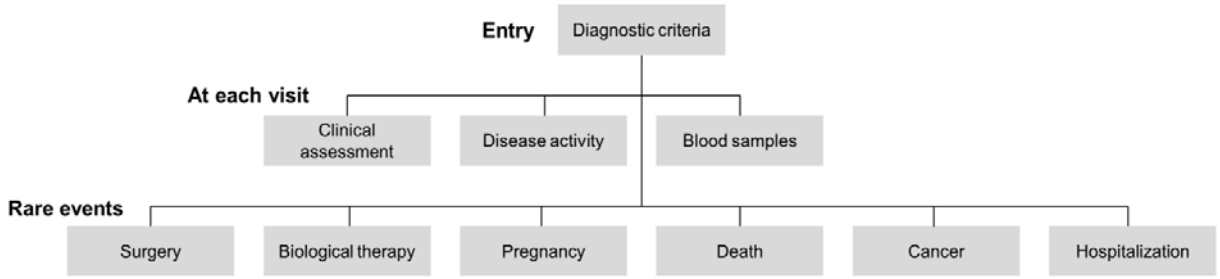


Figure 1. Schematic outline of clinical web schemes in the EpiCom database.

the occurrence and natural course of disease[27]. Since their patient populations are unselected they harbour the whole spectrum of disease severity, and furthermore can elucidate the effectiveness regarding medication and surgery in a community setting. Due to difficulties in executing and maintaining population-based cohorts the capability of performing this type of study is limited in most countries. In Denmark there is a long tradition of conducting population-based cohort studies because of the Copenhagen County cohort[5,6,11,28,29], which was founded in 1958 by Professor Povl Riis and later evolved into the Danish Crohn Colitis Database (DCCD)[30].

In 1988 the European Collaborative study group on Inflammatory Bowel Disease (EC-IBD) was initiated as a collaboration between 20 centres from 12 countries that collected the first European population-based inception cohort between 1991 and 1993[31]. The EC-IBD study found a North-South gradient in Europe, with higher incidences in Northern Europe, but failed to provide an explanation for the geographical distribution of the diseases[32], possibly because countries from Eastern Europe were not included in the study. In 2006 Pia Munkholm became the head of EC-IBD and under her leadership the EC-IBD was assimilated with the European Crohn's and Colitis Organisation (ECCO) to form the Epidemiological Committee (EpiCom). Furthermore, Munkholm and colleagues took the initiative to establish a new collaboration of IBD centres across Europe, this time including centres from both Eastern and Western Europe. Together with Ebbe Langholz and the author, who was appointed the first PhD student within this novel collaboration, Munkholm took the lead in creating a new population-based inception cohort and investigating the occurrence and disease course of IBD in Europe.

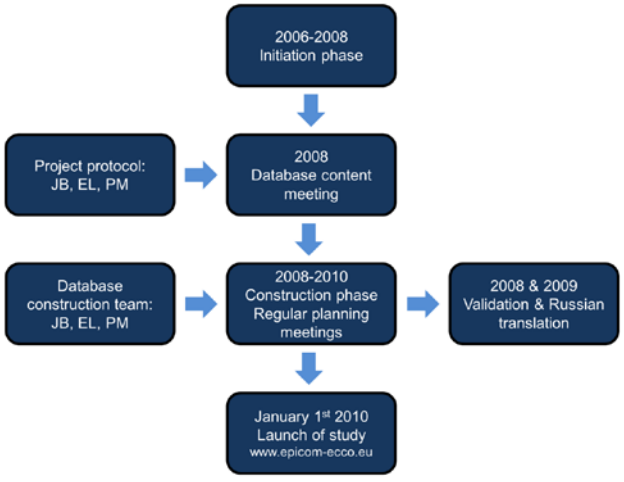


Figure 2. Construction process of the EpiCom database (JB, Johan Burisch; EL, Ebbe Langholz; PM, Pia Munkholm)

2. AIMS

The primary aim of the present thesis was to create a new European population-based inception cohort in order to investigate whether an East-West gradient in the incidence of IBD exists in Europe. A further aim was to construct a secure and entirely web-based epidemiological database for the purpose of remote data capturing.

Secondary aims, addressed after one year, were to investigate possible differences throughout Europe in respect of:

- Initial clinical presentation
- Disease course, including hospitalization, surgery, mortality and cancer
- Choices of medical treatment, including biological agents
- Occurrence and types of environmental factors present prior to diagnosis
- Health care costs
- Health-related quality of life
- Quality of care.

3. METHODS

3.1 STUDY CENTRES

Following an initial meeting in Vienna in 2006 and an announcement in an ECCO newsletter[33], 31 centres from 14 Western and eight Eastern European countries covering a total background population of approximately 10.1 million people (6.8 million from Western and 3.3 million from Eastern Europe), agreed to participate in this study. Nine centres participated both as paediatric and adult centres (Herlev, Funen, Ioannina, Vigo, Northern Italy, Prague, Southern Estonia, and Veszprem Province). Two separate centres from Chisinau, Moldova participated, an adult centre and a paediatric centre (Appendix). The classification of centres as being situated in either Western or Eastern European countries was based on the socio-economic status of that country before 1990.

A well-defined primary catchment area with up-to-date population data, including age and gender distribution, was a prerequisite for participation. Similarly, participation required an established network of gastroenterologists, colorectal surgeons and general practitioners (GPs) within the up-take area who were contacted twice during the inclusion period to ensure complete coverage and inclusion of patients. Local patient self-help groups were approached where possible. Ten centres (32%) reported having organised population-based cohorts before.

3.2 PROJECT STEERING

A study steering committee (JB, EL, PM) drafted the protocol based on the results of a preparatory meeting in 2008 that was then agreed upon by the whole study group. Daily operation of the study – including queries from study participants, reminders

about upcoming deadlines, handling of problems with the database, and data management – was managed by the author. Twice-yearly study group meetings have been organized by the study steering committee since 2006, during which participants have been educated in case ascertainment in order to achieve consistency of methods used as well as in how to use and enter data in the EpiCom database described below.

3.3 THE EPICOM DATABASE

For the purposes of this study and in order to facilitate data acquisition by the participants as well as to centralize data storage, a secure, user-friendly, tailor-made, web-based epidemiological database was constructed. The EpiCom database[34] was designed on the basis of the DCCD[30] as an epidemiological database focusing primarily on academic and epidemiological content to be used for online registration[35] of the various forms used in the EpiCom-project, mentioned below. The data was stored in a secure database engine, including backup, and was secured by the WinLog3 Security System developed by the Danish company HD-Support LLC, Denmark[36], in cooperation with the Danish Data Protection Agency[37]. To ensure anonymity, patients were only registered by date of birth and by a unique patient-ID number. Participating centres had access to their own data only. Access to the database required a yearly fee (for user administration, user support, the hosting of the EpiCom-server) from each centre.

The database was built around ten clinical schemes covering several aspects of the IBD disease course (Figure 1). The diagnostic criteria scheme contained data regarding type of diagnosis, disease classification, diagnostic procedures, patient demographic details and initial treatment. Schemes used at each patient visit included disease activity, blood sample scheme as well as a clinical assessment scheme regarding disease status, treatment, and examinations performed since last visit. There was no bio-banking of blood, tissue or other biological materials. Events such as surgery, biological therapy, death etc., were registered in a separate scheme throughout the study period. Development of the database was carried out by a database construction team in cooperation with HD-support, during a two-year period from 2008 to 2010 (Figure 2). After an initial meeting with the whole study group regarding content in 2008, the database was programmed while at the same time released and continually updated for the database construction group to test and comment on. These issues were then discussed with all EpiCom-members and comments and additional suggestions were implemented. After having secured a certain number of key features, a validation release was provided for all participants, allowing them to test the database, offer comments on the design, and report defects[34].

The database was validated twice (December 2008 and June 2009) by participants using hypothetical IBD cases in order to test content and usability. Each validation round was followed by corrections of reported defects or implementation of suggestions and comments. Overall satisfaction with the database, as well as general applicability, was found to be good after the second validation round, despite participants reporting the database to be time-consuming to use[34]. After the satisfactory validation of the database the feature list was frozen, preventing further changes or additions to its list of features.

3.4 CASE DEFINITION AND INCIDENCE

During a one-year inclusion period all incident cases diagnosed with CD, UC or IBDU between 1 January and 31 December 2010 and living in the predefined catchment areas at the time of diagnosis were prospectively included in the cohort. Cases were required to meet the Copenhagen Diagnostic Criteria for IBD concerning clinical symptoms, endoscopic or radiological evidence or mucosal biopsies:

Copenhagen Diagnostic Criteria for CD (at least two of the criteria present)[5]:

1. History of abdominal pain, weight loss and/or diarrhoea for more than three months
2. Characteristic endoscopic findings of ulceration (aphthous lesions, snail track ulceration) or cobble stoning *or* radiological features of stricture or cobble stoning
3. Histopathology consistent with Crohn's disease (epitheloid granuloma of Langerhans type or transmural discontinuous focal or patchy inflammation)
4. Fistula and/or abscess in relation to affected bowel segments.

Copenhagen Diagnostic Criteria for UC (all three of the criteria present)[6]:

1. History of diarrhoea and/or rectal bleeding and pus for more than one week or repeated episodes
2. Characteristic endoscopic findings of continuous ulceration, vulnerability or granulated mucosa
3. Histopathology consistent with ulcerative colitis (neutrophils within epithelial structures, cryptitis, crypt distortion, crypt abscesses).

Cases in which not all criteria for either CD or UC were fulfilled and yet subsequent relevant IBD treatment was necessary were classified as IBD Unclassified (IBDU)[11]. Infectious gastroenteritis, endamoeba and cancer had to be ruled out. Fulfilment of these criteria was assessed by the participating physicians and gastroenterologists. Cases of patients younger than 15 years were included as paediatric patients in the paediatric centres, with the exception of the centre from the Czech Republic, which included patients younger than 18 years. The age limit of 15 years was the referral age and was decided upon by agreement between all centres.

3.5 CLASSIFICATIONS OF DISEASE AND TREATMENT

Disease phenotype classification by disease extent for UC and by disease location and behaviour for CD were defined according to the Montreal classification[38]. This classification has been shown to have good overall inter-observer agreement[39,40], and thus was found suitable for a multicentre setting. Surgery was defined as total or subtotal colectomy for UC and small or large bowel resections for CD due to IBD, while fistulectomies, abscess drainage etc. were excluded from this category. Cause of death and type of cancer were categorized according to the 10th revision of the International Classification of Diseases[41].

Treatment was grouped according to ascending severity: 5-aminosalicylates (5-ASA) (oral and/or topical 5-ASA treatment ± topical steroids), glucocorticosteroids (GCS) (oral steroids ± 5-ASA or topical steroids), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine or methotrexate ± steroids), biologicals (infliximab or adalimumab in combination with any of the above), and surgery (regardless of medical treatment prior to surgery). Immunomodulators were combined in one category since 94% of patients received thiopurines (azathioprine and 6-mercaptopurine).

Treatment (medical or surgical) initiated during a hospitalization was defined as the highest treatment step reached within 14 days from the day of hospitalization. Induction therapy was defined as

treatment initiated within the first three months after diagnosis. Due to the slow onset of action of thiopurines[42] for the analysis of induction therapy the steps relating to steroids (oral steroids ± azathioprine, 6-mercaptopurine, 5-ASA or topical steroids) and immunomodulators (methotrexate ± steroids, azathioprine, 6-mercaptopurine, cyclosporine ± steroids) where defined differently.

3.6 DISEASE ACTIVITY AND SEVERITY

Disease activity was measured using the *Simple Clinical Colitis Index* (SCCAI)[43] for UC and the *Harvey Bradshaw Index* (HBI)[44] for CD patients. A SCCAI score of ≤2 was defined as remission, 3-4 as mild/moderately active disease and ≥5 as severely active disease[45] for UC patients. In CD a HBI score of <5 was defined as remission, 5-7 as mildly active disease, 8-16 as moderately active disease and ≥16 as severely active disease[46]. If data regarding disease activity were insufficient, patients were categorized as having a severe course of disease or not after 12 months of follow-up. Thus, in UC a severe disease course was defined as any disease extent and a need for high dose GCS (0.5–1 mg/kg), and/or immunomodulators, and/or biologicals, and/or surgery. Severe CD was defined as the need for immunomodulators, and/or biologicals, and/or surgery within the first year after diagnosis.

3.7 QUALITY OF LIFE

The *Short Inflammatory Bowel Disease Questionnaire* (SIBDQ) and the *Short Form 12* (SF-12) were used to assess the patient-reported HRQoL. The SIBDQ is a disease-specific questionnaire consisting of ten questions covering four dimensions: bowel, systemic, emotional and social[47]. The questionnaire is scored on a seven-point scale with higher scores indicating a better HRQoL. The total score ranges from 10 (worst health) to 70 (best health), good HRQoL was defined as a score above 50 points[47]. Responders were defined as patients experiencing an improved SIBDQ score during follow-up from ≤ 50 to >50. The SF-12 is a generic HRQoL questionnaire of 12 questions grouped into a physical and a mental component summary score (PCS and MCS) and eight multi-item scales: Physical Functioning (PF), Role limitation due to Physical health (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role limitations due to Emotional problems (RE), and Mental Health (MH). The SF-12 scores were converted according to the manual[48] to achieve a mean score of 50 and a standard deviation of 10 in the 1998 general US population. The US population was chosen as reference population since it has been shown to have good equivalence with country-specific scores in ten Western European countries[49,50].

3.8 ENVIRONMENTAL FACTORS

Environmental factors prior to the development of IBD were assessed using a questionnaire developed and proposed by the International Organisation of Inflammatory Bowel Diseases (IOIBD)[51]. The questionnaire included 87 questions covering 25 different topics suspected to be environmental risk factors for CD and/or UC. The questionnaire has previously been used in population-based IBD cohorts[52,53] and was evaluated in a case-control study[54]. In order to analyse the impact of the environmental factors on disease presentation at diagnosis and on disease course, items were grouped by the following parameters: smoking status at diagnosis, appendectomy before age 20, tonsillectomy before age 20, use of oral contraceptives, breastfeeding during infancy, childhood infections (measles, pertussis, rubella, chickenpox, mumps, and/or scarlet fever), vaccinations (tuberculosis, pertussis, measles, rubella, diphtheria, tetanus, and/or polio), high sugar consumption (≥2 of the following: sugar in coffee, sugar in tea, daily intake of soft drinks, sugar on breakfast cereals, sugar on porridge), high fibre intake (daily intake of ≥3 of the following categories: fruit, vegetables, whole meal bread, ≥4 pieces of bread, cornflakes, muesli), fast food consumption, high intake of caffeine (≥2 cups of coffee or tea per day), daily physical activity, access to running water at home, and IBD in first-degree relatives.

3.9 QUALITY OF CARE

Conditions regarding the level of QoC were assessed using a questionnaire by choice constructed by IBD nurses in the EpiCom group on the basis of the ECCO health quality of care consensus[55]. The questionnaire consists of 16 questions with five care dimensions: two questions regarding the time interval between the onset of symptoms and diagnosis, patients' and doctors' delay and the time elapsed from the first consultation with the general practitioner to when the patients were referred to a gastroenterologist; six questions concerning the patients' knowledge about their disease before and after diagnosis, their sources of information in the health care system, and patient self-searching information; three questions regarding whether patients received education about IBD; four questions concerning empathy and the courtesy of the members of the health care system and whether they were perceived to be spending enough time with the patients and answering their questions sufficiently; and finally one question concerning the ease of access to health care providers.

3.10 CALCULATIONS OF COSTS

Resource utilization was assessed using the Danish Health Costs Register (Diagnosis-related group, DRG)[56] representing the mean costs for hospital and out-patient procedures in Denmark, as well as the prices for medicine in the capital region of Denmark[57]. As prices for medicine were only available for the year 2013 the DRG charges for 2013 were used, since price differences compared to 2010 were deemed to have no significant effect on the overall comparison. Prices were converted from Danish Kroner to Euros[58]. Indirect costs of IBD patients (transport costs, loss of study or work time etc.) were not recorded.

Hospital and out-patient procedures, as well as therapies for IBD, were grouped according to four categories: 1) Diagnostic procedures (upper gastrointestinal endoscopy, colonoscopy, sigmoidoscopy, endoscopic ultrasound, enteroscopy, capsule endoscopy, and multiple radiological examinations, including ultrasound, barium studies, computerized tomography (CT) and magnetic resonance imaging (MRI and MRE)); 2) standard therapy (5-ASA (oral and topical), GCS (systemic/oral, locally-acting steroids, and budesonide), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine and methotrexate)); 3) biological therapy (infliximab or adalimumab, costs for in-hospital administration of infliximab were incorporated); and 4) IBD surgery (including costs for pathology). Antibiotics, nutritional supplements, iron preparation and supplementary preparations were documented but excluded from the analysis. Similarly, various stool and blood tests were omitted from the calculations; however, the excluded items had little monetary effect on the overall outlay on treatment.

3.11 DATA COLLECTION AND FOLLOW-UP

Included patients were followed prospectively every third month in the out-patient clinic from diagnosis and throughout a minimum follow-up period of 12±3 months. To encourage the re-

searchers in entering the data, automatic feedback to the investigator and centres was provided via the project website[35] as a running overview bar of the cumulative number of included patients and current incidence rate. Data regarding patient demographics (socio-demographic details, level of education, current occupation, smoking habits, and oral contraceptive use), disease activity, disease classification, current medical therapy, including biological agents, surgery, hospitalization, cancers and deaths, were collected prospectively.

Patient-reported questionnaires regarding HRQoL were administered twice during the follow-up period: first, at time of diagnosis ± three months, and then at nine to 24 months follow-up. This interval was chosen in order to compensate for variations in follow-up visits due to holidays, weekends and personal reasons of the patients and since centres either chose to follow-up patients for only twelve months for this study or until the end of the year 2011 for local practical reasons. The questionnaires regarding environmental factors and quality of care were administered at diagnosis and at follow-up, respectively. If available, the relevant translated versions of the questionnaires were used. Patients were asked to answer the questionnaires either by themselves or, depending on their educational level and whether local translations of the questionnaire existed, during an interview by the physician or IBD specialist trained nurses at an out-patient visit. All clinical data, as well as questionnaire responses, were entered in the EpiCom database[34] by the physicians or IBD specialist trained nurses.

3.12 DATA VALIDITY

Several measures were used to secure the quality and validity of the recorded data. All centres were required to reach an incidence rate of a minimum 60% of previously reported rates in order to avoid exclusion from the study. Furthermore, centres with fewer than 60% of their patients having sufficient follow-up data were excluded from the analysis on disease course during the initial year after diagnosis. This practice was in accordance with the previous EC-IBD cohort study[59]. The database contained built-in control and validation tests as well as locked diagnostic criteria. All data were validated during a six-month period by the principal investigator and centres asked to provide missing data when necessary. Random audits of case ascertainment and data quality were performed at 23 centres, followed by corrections if necessary.

3.13 STATISTICAL ANALYSIS

All data were extracted from the EpiCom-database[34] as comma-separated values (CSV) files. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) and for the cost analysis using SPSS software v. 18 (SPSS Inc.,

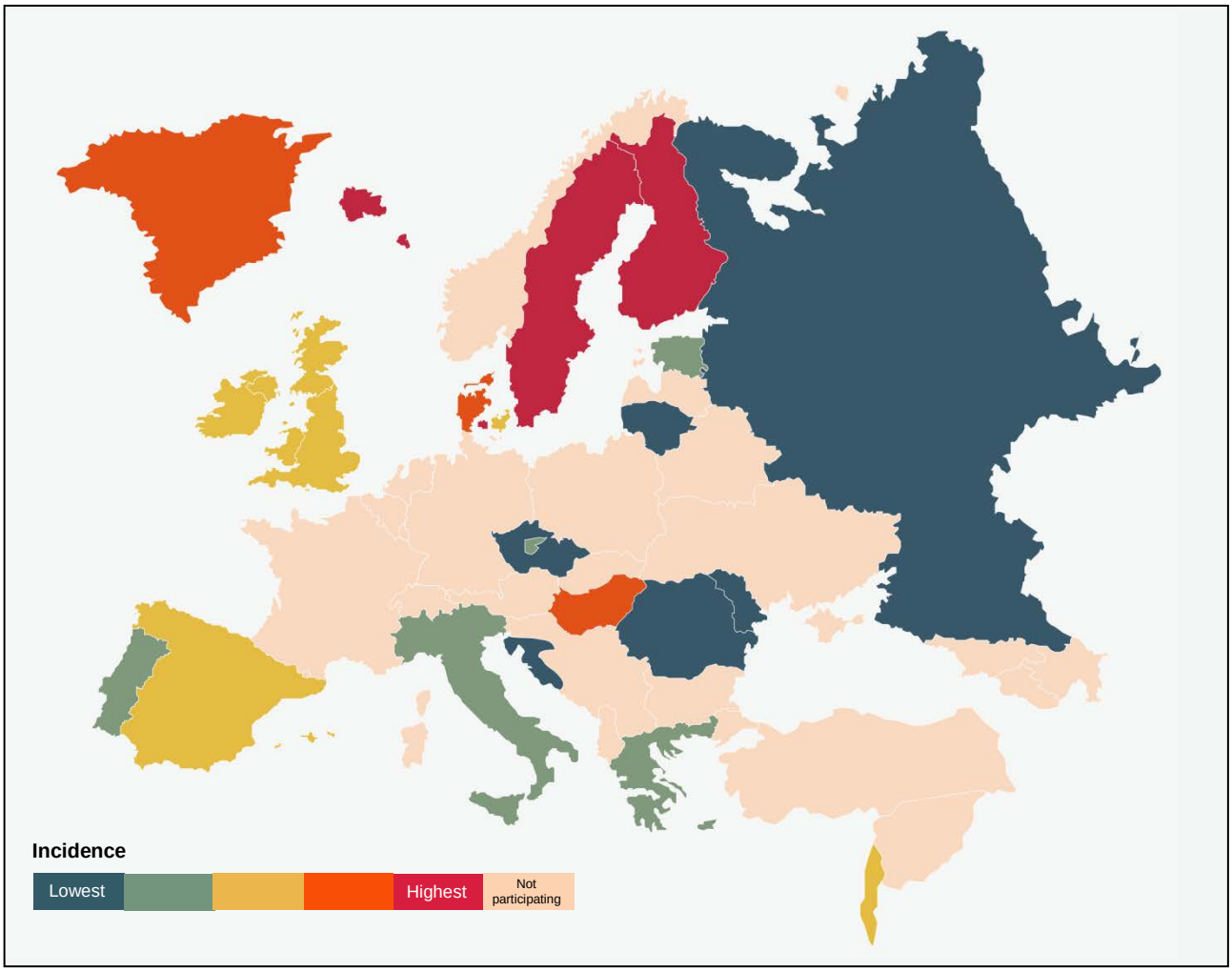


Figure 3. Incidence rates (/100,000) of cases aged 15 years or older for inflammatory bowel disease (IBD) in the EpiCom-study areas as in Europe in 2010

Chicago, IL, USA). Categorical variables are summarized as proportions. Results for continuous variables are expressed as median (range) unless otherwise stated, while HRQoL scores are expressed as mean (standard deviation, SD). Continuous variables were analysed by Student's t-test or one-way ANOVA. Categorical data were analysed using χ^2-test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered to be statistically significant.

3.13.1 Incidence

Age, gender and disease-specific incidence rates (per 100,000) for each study area were calculated by dividing the number of new cases in each category of age and gender by the corresponding estimated number of person years at risk based on the population statistics for each area. Age- and gender-standardized incidence rates for the adult population were obtained using the European Standard population[60] using the age groups 15-44 years, 45-64 years and 65+ years. The 95% confidence interval (CI) for incidence rates was calculated on the assumption of a Poisson distribution. The test of equality of the incidence rates across the regions in Europe was based on the Poisson distribution. The gross domestic product (GDP) or rather the purchasing power parity (PPP) version of GDP, which expresses GDP in terms of the 'international' dollar, a technique used to adjust for differences in purchasing power within each country, were obtained for 2011 from the World Bank data service[61]. Log-linear Poisson regression was used to analyse incidence rates as depending on age at diagnosis, gender, geographic region, and GDP.

3.13.2 Disease course

Associations between surgery, hospitalization, and biological treatment and multiple covariates (age, gender, diagnosis, geographic region, disease behaviour for CD, disease extent for UC, initial treatment (highest step reached within the first three months from diagnosis), smoking status) were analysed by Cox regression analyses using the proportional hazards assumption and associations were visualized by Kaplan-Meier plots. Only events occurring after diagnosis and among patients being followed-up were included in the Cox regression analysis.

3.13.3 HRQoL

Differences in HRQoL data between groups were analysed using standard non-parametric methods. The total SIBDQ score was rescaled with 10/9 or 10/8 if one or two questions were missing, while no total score was calculated if more than two questions were missing. Dimensions containing missing data were not calculated. Regarding SF-12, only complete cases were calculated and included in the analysis. Changes in mean SIBDQ and SF-12 (PCS and MCS) scores were analysed using linear normal analysis of covariance (ANCOVA). SIBDQ responders were analysed by logistic regression with backwards elimination of insignificant factors regarding the following predicting factors: socio-demographic characteristics, disease classification at diagnosis, hospitalization, surgery, biological therapy, severe disease course, highest treatment step, and extra-intestinal manifestations at diagnosis.

3.13.4 Environmental factors

Prognostic environmental factors on disease classification at diagnosis, hospitalization, surgery, biological therapy, severe disease course, and extra-intestinal manifestations at diagnosis were identified using multivariate logistic regression. The impact of environmental factors on age of diagnosis was analysed with simple multivariate linear regression. Gender, age, and geographic region were included in the analysis, together with disease classification, when relevant, as these were considered confounding variables. Childhood infections and vaccinations were excluded from the analysis as they were highly correlated with year of birth.

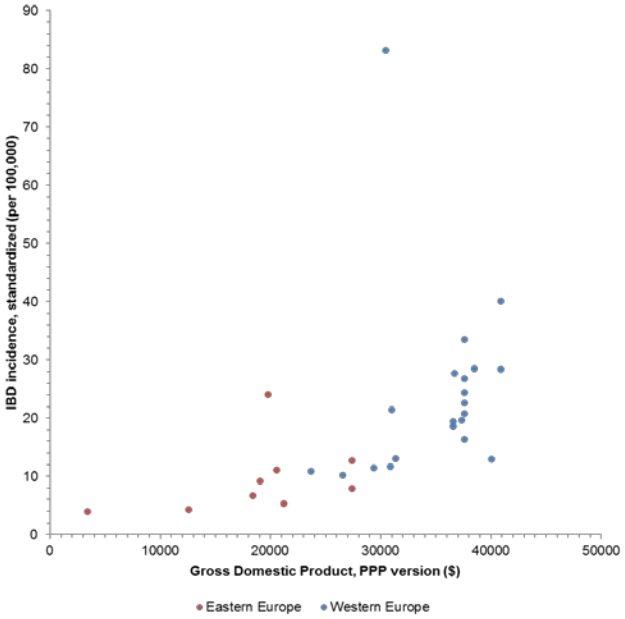


Figure 4. Inflammatory bowel disease (IBD) standardised incidence rates versus 2010/2011 purchasing power parity (PPP) version of gross domestic product (GDP) in 9 Eastern and 21 Western European centres. The two regions were almost separate in terms of GDP and incidence rates increased with GDP.

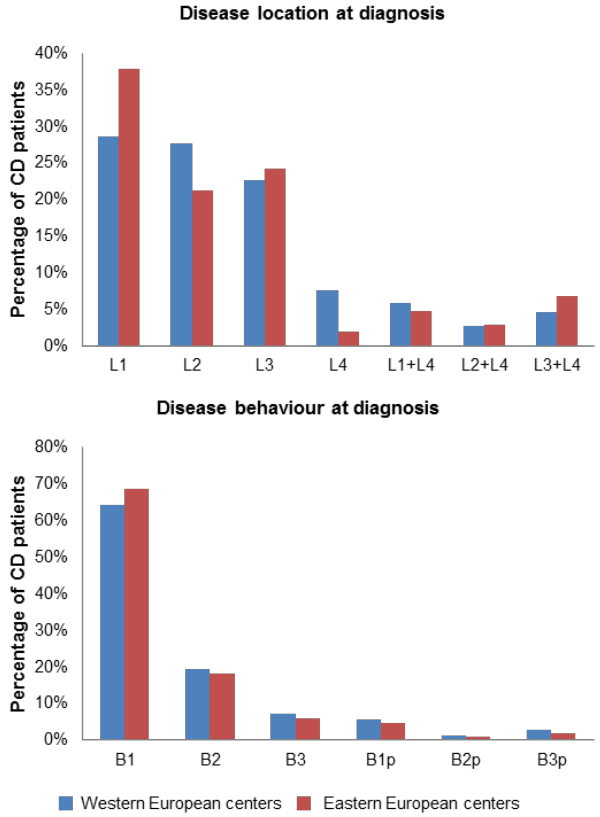


Figure 5. Disease location and behaviour at diagnosis for adult patients with Crohn's disease (CD) did not differ between Eastern and Western Europe (p=NS).

Table 1. Incidence rates per 100,000 for inflammatory bowel disease, Crohn's disease, ulcerative colitis and inflammatory bowel disease unclassified in Europe for patients aged 15 years or older in 2010.

	No. of patients	IBD crude	IBD adj. (SE)	CD crude	CD adj. (SE)	UC crude	UC adj. (SE)	IBDU crude	IBDU adj. (SE)
Western European centres									
Cyprus, Nicosia	27	11.2	11.4 (2.2)	6.2	6.3 (1.6)	2.9	3.0 (1.1)	2.1	2.2 (1.0)
Denmark, Aarhus	55	21.2	20.7 (2.8)	8.5	8.2 (1.8)	10.8	10.6 (2.0)	1.9	1.8 (0.8)
Denmark, Amager	23	17.2	16.3 (3.4)	5.2	4.8 (1.8)	7.5	7.4 (2.4)	4.5	4.1 (1.7)
Denmark, Funen	123	30.7	33.4 (3.1)	10.7	11.4 (1.8)	18.7	20.1 (2.4)	1.2	1.4 (0.7)
Denmark, Herlev	48	22.4	24.4 (3.6)	6.5	7.0 (1.9)	7.5	8.3 (2.1)	8.4	9.2 (2.2)
Denmark, Herning	49	21.2	22.5 (3.3)	6.5	7.1 (1.9)	12.6	13.0 (2.5)	2.2	2.3 (1.1)
Denmark, Viborg	37	24.6	26.7 (4.5)	8.6	9.6 (2.7)	14.6	15.7 (3.4)	1.3	1.4 (1.0)
Faroe Islands	31	81.5	83.1 (15.0)	10.5	11.1 (5.6)	31.5	31.8 (9.3)	39.4	40.2 (10.5)
Finland, Pirkanmaa	107	26.2	27.7 (2.7)	4.4	5.0 (1.2)	17.1	18.0 (2.2)	4.7	4.7 (1.1)
Greece, Ioanninia	15	9.2	10.2 (2.6)	3.1	3.5 (1.6)	5.5	6.0 (2.0)	0.6	0.7 (0.7)
Greenland	9	24.0	19.6 (6.6)	0.0	0 (0)	24.0	19.6 (6.6)	0.0	0 (0)
Iceland	72	28.7	28.5 (3.4)	5.6	5.6 (1.5)	17.9	17.8 (2.7)	5.2	5.1 (1.4)
Ireland, Adelaide and Meath	36	13.2	12.9 (2.2)	4.8	4.3 (1.2)	4.4	4.2 (1.2)	4.0	4.4 (1.4)
Israel, Beer Sheva	51	13.2	13.0 (1.9)	8.6	8.4 (1.5)	4.4	4.4 (1.1)	0.3	0.2 (0.2)
Italy, Northern Italy	182	10.9	11.6 (0.9)	3.9	4.3 (0.5)	6.1	6.4 (0.7)	0.8	0.9 (0.3)
Portugal, Vale de Sousa	31	11.1	10.8 (2.0)	7.2	7.0 (1.6)	3.9	3.8 (1.2)	0.0	0 (0)
Spain, Vigo	102	20.4	21.4 (2.1)	10.2	10.8 (1.5)	9.0	9.4 (1.4)	1.2	1.2 (0.5)
Sweden, Linköping	55	38.3	40.0 (5.4)	9.8	10.1 (2.7)	16.0	16.5 (3.5)	12.5	13.5 (3.2)
Sweden, Örebro	39	26.5	28.3 (4.6)	7.5	8.3 (2.5)	15.6	16.1 (3.4)	3.4	3.9 (1.8)
UK, Brent and Harrow	76	19.9	19.3 (2.2)	2.6	2.4 (0.8)	15.9	15.6 (2.0)	1.3	1.3 (0.6)
UK, Hull and East Yorkshire	91	18.1	18.6 (2.0)	8.4	8.9 (1.4)	8.2	8.3 (1.3)	1.6	1.4 (0.5)
Eastern European centres									
Croatia, Zagreb	12	6.3	6.6 (1.9)	3.1	3.3 (1.3)	3.1	3.3 (1.4)	0.0	0 (0)
Czech Republic, Prague	22	12.2	12.7 (2.8)	5.5	5.6 (1.8)	5.5	5.8 (1.9)	1.1	1.3 (0.9)
Czech Republic, South Bohemia	42	7.7	7.9 (1.2)	3.8	3.9 (0.9)	3.8	3.9 (0.9)	0.0	0 (0)
Estonia, Southern Estonia	30	10.3	11.0 (2.0)	5.2	5.4 (1.4)	5.2	5.7 (1.5)	0.0	0 (0)
Hungary, Veszprem province	58	23.0	24.0 (3.2)	11.5	12.0 (2.2)	10.3	10.7 (2.1)	1.2	1.3 (0.7)
Lithuania, Kaunas	32	8.5	9.1 (1.6)	2.4	2.6 (0.9)	6.1	6.5 (1.4)	0.0	0 (0)
Moldova, Chisinau	10	4.3	3.9 (1.2)	0.4	0.4 (0.4)	3.9	3.5 (1.2)	0.0	0 (0)
Romania, Timis	24	4.1	4.2 (0.9)	1.7	1.7 (0.5)	2.4	2.5 (0.7)	0.0	0 (0)
Russia, Moscow	26	5.1	5.3 (1.1)	0.8	0.9 (0.5)	4.1	4.2 (0.9)	0.2	0.2 (0.2)
Regional incidence rates	**No. patients**		**IBD (95% CI)**		**CD (95% CI)**		**UC (95% CI)**		**IBDU (95% CI)**
All Western European centres	1259		18.5 (17.5-19.5)*		6.3 (5.7-6.9)*		9.8 (9.1-10.6)*		2.4 (2.0-2.8)*
All Eastern European centres	256		8.1 (7.2-9.2)		3.3 (2.7-4.0)		4.6 (3.9-5.4)		0.2 (0.1-0,4)
All centres	1515		15.2 (14.4-16.0)		5.4 (4.9-5.8)		8.2 (7.6-8.7)		1.7 (1.4-1.9)

* difference in incidence between the geographic regions p<0.01.

CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis; SE, standard error.

Table 2. Crude incidence rates per 100,000 for inflammatory bowel disease, Crohn's disease, ulcerative colitis and inflammatory bowel disease unclassified in Europe for patients aged <15 years in 2010.

	No. of patients	IBD	CD	UC	IC
Western European centres					
Denmark, Funen	6	7.1	4.7	2.4	0.0
Denmark, Herlev	4	8.1	2.0	2.0	4.0
Faroe Islands	1	9.4	0.0	9.4	0.0
Greece, Ioanninia	0	0.0	0.0	0.0	0.0
Italy, Northern Italy	4	1.5	0.4	1.1	0.0
Spain, Vigo	5	6.7	4.0	2.7	0.0
Eastern European centres					
Czech Republic, Prague	3	8.0	2.7	2.7	2.7
Estonia, Southern Estonia	3	5.6	5.6	0.0	0.0
Hungary, Veszprem	2	4.7	2.3	2.3	0.0
Lithuania, Kaunas	0	0.0	0.0	0.0	0.0
Moldova, Chisinau	17	2.9	0.2	2.7	0.0
All Western European centres, median	20	6.9	1.2	2.2	0.0
All Eastern European centres, median	25	4.7	2.3	2.3	0.0
All European centres, median	45	5.6	2.0	2.3	0.0

3.13.5 Analysis of resource utilization and costs

The cost of each resource was calculated per patient by multiplying the price of that resource by the quantity of resource used during follow-up. Results are given rounded to the nearest whole Euro. Statistical differences between study population characteristics and costs were analysed using one-way ANOVA. The dependent variable was total health care cost, and the independent variables were age at diagnosis, type of diagnosis, and type of treatment (standard non-anti-TNF medication, biological therapy, or surgery).

3.14 ETHICAL CONSIDERATIONS

The study was approved by the local ethical committees according to local regulations. Depending on local regulations patients signed a consent form prior to data incorporation regarding clinical data and/or questionnaires.

4. RESULTS

4.1 THE WEST-EAST INCIDENCE GRADIENT IN EUROPE IN 2010

During the one-year inclusion period in 2010 a total number of 1,515 patients aged 15 years or older were diagnosed with IBD, 535 (35%) with CD, 813 (54%) with UC, and 167 (11%) with IBDU. The majority of patients (1,259 (83%)) were diagnosed in Western European centres. Paediatric IBD was diagnosed in 45 patients, 15 (33%) with CD, 27 (60%) with UC, and three (7%) with IBDU. Regional and centre-wise annual crude, as well as age- and gender-adjusted, incidence rates are shown in Tables 1 and 2, centre-wise incidence rates for IBD are depicted in Figure 3. The highest incidence of IBD was observed on the Faroe Islands, at 81.5 per 100,000. In adult patients a West-East incidence gradient of two was found in Europe as combined annual incidence rates for IBD (incidence rate ratio, (IRR) = 2.3 CI95%: 2.0-2.6), CD (IRR = 1.9 CI95%: 1.5-2.4), and UC (IRR = 2.1 CI95%: 1.8-2.6) in all Western European centres were twice as high as in Eastern Europe. Annual

Table 3. Relative incidence rate ratio (95% CI) according to gross domestic product, gender, age at diagnosis and geographic region in a European inception cohort.

	IBD	CD	UC
GDP (PPP) per 10,000 int.$	1.7 (1.3-2.2)*	1.5 (1.2-2.0)*	1.6 (1.3-2.0)*
Gender (female vs. male)	0.8 (0.7-0.9)*	0.9 (0.7-1.0)	0.8 (0.7-0.9)*
Age (15-44 yr. vs. 65+ yr.)	2.3 (2.0-2.8)*	3.1 (2.3-4.2)*	2.0 (1.6-2.5)*
Age (15-44 yr. vs. 45-64 yr.)	1.6 (1.4-1.8)*	1.9 (1.6-2.4)*	1.5 (1.2-1.7)*
Age (45-64 yr. vs. 65+ yr.)	1.4 (1.2-1.7)*	1.6 (1.1-2.3)*	1.4 (1.1-1.8)*
Region (East vs. West)	0.4 (0.2-0.7)*	0.5 (0.3-0.8)*	0.5 (0.3-0.8)*

* Rate ratios excluding 1.0 (p<0.01)

IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

incidence rates correlated with the GDP of the respective country as the highest incidences were observed in countries with high GDP, i.e. Western European centres (Figure 4). This was confirmed in the regression analysis, where high GDP and being a Western European centre were predictive of high incidence rates (Table 3). High concordance prohibited the separation of the effects of GDP and geographic region, and the variation in rates could thus be ascribed to either factor.

4.2 PATIENT CHARACTERISTICS ARE SIMILAR IN EASTERN AND WESTERN EUROPE

No regional differences in terms of socio-demographic characteristics or diagnostic delay (time from onset of symptoms to diagnosis) were found, with the exception of educational status in adult IBD patients (Tables 4 and 5). In both regions more CD patients than UC patients were current smokers at the time of diagnosis, while the opposite was true for former smokers (p<0.01). Disease classification at diagnosis for adult CD and UC patients was similar in Eastern and Western Europe (Figures 5 and 6).

4.3 CHOICES OF DIAGNOSTIC INVESTIGATIONS DIFFER IN EUROPE

Regional differences were found regarding the diagnostic procedures performed in order to obtain the diagnosis of IBD (Table 6). While all UC patients were diagnosed using endoscopy, full colonoscopy was only performed in 78% of UC patients from Western Europe, compared with 90% of UC patients from Eastern European countries (p<0.01). The remaining patients had a sigmoidoscopy performed (proctosigmoiditis patients, where the investigator reached normal tissue). The proportion of CD patients having colonoscopy (93% in Western and 96% in Eastern Europe) and IBDU patients (74% and 100%, respectively) was similar in both geographic regions. Significantly more CD (35% vs. 10%, p<0.05) and UC (10% vs. 3%, p<0.05) patients in Eastern Europe had an upper endoscopy performed as part of their diagnostic investigations, while more Eastern European UC patients had a bowel X-ray performed (12% vs. 3%, p<0.05).

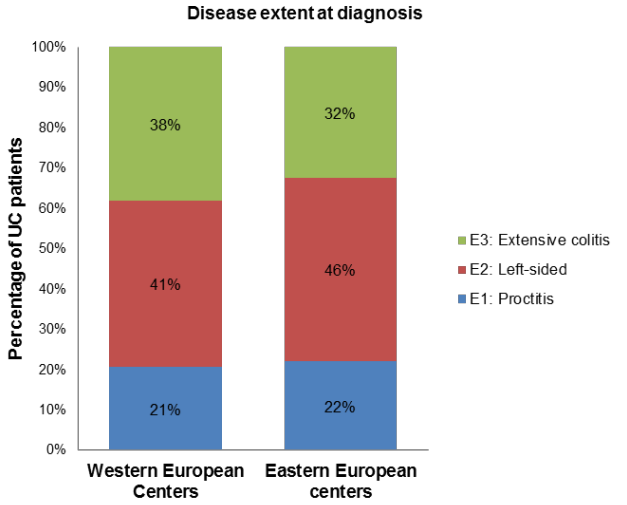


Figure 6. Extent of disease at diagnosis for adult patients with ulcerative colitis (UC) did not differ between Eastern and Western Europe (p=NS).

4.4 COURSE OF DISEASE DURING THE INITIAL YEAR FOLLOWING DIAGNOSIS

The initial disease course was investigated in adult patients (aged 15 year or older at diagnosis). Two centres from Western Europe

	Western European Centres			Eastern European Centres		
	CD	UC	IC	CD	UC	IC
No. of patients (%)	430 (34%)	668 (53%)	161 (13%)	105 (41%)	145 (57%)	6 (2%)
Males (%)	220 (51%)	375 (56%)	78 (48%)	63 (60%)	82 (57%)	4 (67%)
Age, years	38 (16-89)	39 (15-89)	38 (16-84)	32 (15-78)	36 (18-81)	30 (20-34)
Median time to diagnosis, months	4.6 (0-31 yr.)	2.5 (0-21 yr.)	2.4 (0-30 yr.)	3.4 (0-20 yr.)	2.2 (0-5 yr.)	2.7 (0-3 yr.)
Never smoked	170 (43%)	311 (56%)	70 (51%)	39 (38%)	77 (54%)	4 (67%)
Current smoker	142 (36%)	52 (9%)	20 (15%)	39 (38%)	16 (11%)	2 (33%)
Former smoker	88 (21%)	196 (35%)	46 (34%)	25 (24%)	51 (35%)	0 (0%)
Educational status at diagnosis *						
Academic education		191 (18%)			53 (21%)	
Non-academic education		564 (55%)			131 (52%)	
Currently in education		151 (15%)			57 (23%)	
No education		128 (12%)			12 (5%)	
Employment status at diagnosis						
Employed		557 (53%)			137 (54%)	
Self-employed		63 (6%)			12 (5%)	
Unemployed		121 (11%)			26 (10%)	
Student		161 (15%)			42 (17%)	
Retired		157 (15%)			36 (14%)	
Extra-intestinal manifestations at diagnosis						
None		1085 (88%)			221 (85%)	
Skin		19 (2%)			3 (1%)	
Eyes		18 (2%)			3 (1%)	
Joints		86 (7%)			27 (10%)	
Primary Sclerosing Cholangitis (PSC)		5 (0%)			2 (1%)	
Pancreatitis		3 (0%)			2 (1%)	
Other		13 (1%)			3 (1%)	

* difference between geographic regions p<0.05.

Table 4. Demographic characteristics of 1,515 incident adult patients with inflammatory bowel disease.

	Western European Centres			Eastern European Centres		
	CD	UC	IBDU	CD	UC	IBDU
No. of patients (%)	9 (45%)	9 (45%)	2 (10%)	6 (24%)	18 (72%)	1 (5%)
Males (%)	5 (56%)	3 (33%)	1 (50%)	3 (50%)	8 (44%)	1 (100%)
Age, years	11 (6-14 yr.)	12 yr. (1-14 yr.)	10 yr. (7-14 yr.)	10 yr. (2-16 yr.)	4 yr. (1-16 yr.)	9 yr.
Median time to diagnosis, months	4.1 (0.3-12.4)	2.3 (0.6-5.8)	1.9 (1.5-2.2)	3.6 (2.0-17.0)	2.7 (1.2-104.3)	3.5
Disease extent at diagnosis						
Proctitis		3 (33%)			1 (6%)	
Left-sided		1 (11%)			15 (83%)	
Extensive colitis		5 (56%)			2 (11%)	
Disease location at diagnosis						
L1: Terminal ileum	0 (0%)			1 (17%)		
L2: Colon	1 (11%)			3 (50%)		
L3: Terminal ileum + colon	5 (56%)			1 (17%)		
L4: Upper GI	0 (0%)			0 (0%)		
L1+L4	1 (11%)			0 (0%)		
L2+L4	1 (11%)			0 (0%)		
L3+L4	1 (11%)			1 (17%)		
Disease behaviour at diagnosis						
B1: non-stricturing, non-penetrating ± perianal	8 (89%)			5 (83%)		
B2: stricturing ± perianal	0 (0%)			1 (17%)		
B3: penetrating ± perianal	1 (11%)			0 (0%)		

Table 5. Demographic characteristics of 45 incident paediatric patients with inflammatory bowel disease.

	Western European Centres			Eastern European centres		
Adult population	**CD**	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
None	5 (1%)	0 (0%)	1 (1%)	2 (2%)	0 (0%)	0 (0%)
Upper GI endoscopy	43 (10%)*	22 (3%)*	5 (3%)	36 (34%)	14 (10%)	0 (0%)
Colonoscopy	402 (93%)	524 (78%)*	119 (74%)	101 (96%)	130 (90%)	6 (100%)
Proctoscopy/ Sigmoidoscopy	24 (6%)	190 (28%)	60 (37%)	4 (4%)	35 (24%)	1 (17%)
Capsule endoscopy	42 (10%)	1 (0%)	6 (4%)	15 (14%)	0 (0%)	0 (0%)
Trans Rectal Ultrasound	2 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
MRI	76 (18%)	6 (1%)	5 (3%)	12 (11%)	2 (1%)	0 (0%)
CT-scan	144 (33%)	27 (4%)	15 (9%)	26 (25%)	2 (1%)	1 (17%)
Bowel X-Ray	50 (12%)	21 (3%)*	6 (4%)	16 (15%)	18 (12%)	1 (17%)
Paediatric population	**CD**	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Upper GI endoscopy	3 (33%)	0 (0%)	1 (50%)	3 (50%)	6 (33%)	1 (100%)
Colonoscopy	9 (100%)	9 (100%)	1 (50%)	6 (100%)	15 (87%)	1 (100%)
Proctoscopy/ Sigmoidoscopy	0 (0%)	0 (0%)	1 (50%)	0 (0%)	3 (13%)	0 (0%)
Capsule endoscopy	1 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Trans Rectal Ultrasound	1 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MRI	3 (33%)	1 (11%)	0 (0%)	3 (50%)	1 (6%)	0 (0%)
CT-scan	1 (11%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)
Bowel X-Ray	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (6%)	0 (0%)

* difference between geographic regions p<0.05.

Table 6. Diagnostic procedures performed in adult and paediatric patients with inflammatory bowel disease.

(London, UK and Reykjavik, Iceland) were unable to supply sufficient follow-up data and were excluded from this part of the study. Therefore, the follow-up cohort consisted of 1,367 patients (90% of the original adult cohort), 509 (37%) with CD, 710 (52%) with UC, and 148 (11%) with IBDU, from 28 centres. Patient characteristics in the follow-up cohort (Appendix) did not differ from the original cohort.

4.4.1 Change of diagnosis

No patients from Eastern Europe had a change in diagnosis within the first year of follow-up compared to 27 (2.4%) in Western Europe. Four CD patients changed the diagnosis to UC after a median time of eight months, three UC patients changed to CD after a median time of five months and one UC patient to IBDU. Out of 19 IBDU patients, 11 changed diagnosis to UC and eight to CD after a median follow-up of four months. The majority of patients (70%) changed diagnosis after endoscopy. No patients had a change of diagnosis after surgery.

4.4.2 Rates of surgery are similar in Eastern and Western Europe

A total of 77 (15%) CD patients underwent surgery (hemicolectomy, n=5; colectomy, n=3; small bowel including ileocecal resection, n=79) within the first year of disease. No difference in surgery rates was found between Western Europe (n=65; 16%) and Eastern Europe (n=12; 12%) (Figure 7). Twenty-two (3%) UC patients had a colectomy performed. Of those, 20 (4%) came from Western European centres and this was a similar to two (1%) patients from Eastern Europe. Five (4%) patients with IBDU from Western Europe underwent surgery (hemi-colectomy, n=1; colectomy, n=4). A diagnosis of CD patients was associated with a higher risk of surgery (CD vs. UC: hazard ratio (HR) 3.6, 95% CI: 2.1-6.3; p<0.001). Furthermore, disease behaviour in CD (B2 vs. B1: HR 11.3, 95% CI: 4.9-25.9; B3 vs. B1: 18.6, 95% CI: 7.6-45.3; p<0.001) and disease extent in UC were associated with the risk of surgery (E2 vs. E1: HR 2.0, 95% CI 0.2-18.0; E3 vs. E1: HR 7.3, 95% CI: 1.0-55.7; p=0.02) (Figure 8).

4.4.3 Hospitalization rates for CD patients did not differ between regions

IBD-related hospitalizations occurred in 98 (19%) CD patients, 92 (13%) UC patients, and 13 (9%) IBDU patients. In Western Europe, 81 (20%) CD patients were hospitalized for the first time after median 5.1 months (range: 0-15), which was comparable to 17 (16%) CD patients in Eastern Europe (median time to hospitalization: 4.0 months (range: 0-15) (p=0.56) (Figure 7)). The corresponding numbers for UC were 80 (14%) in Western Europe (me

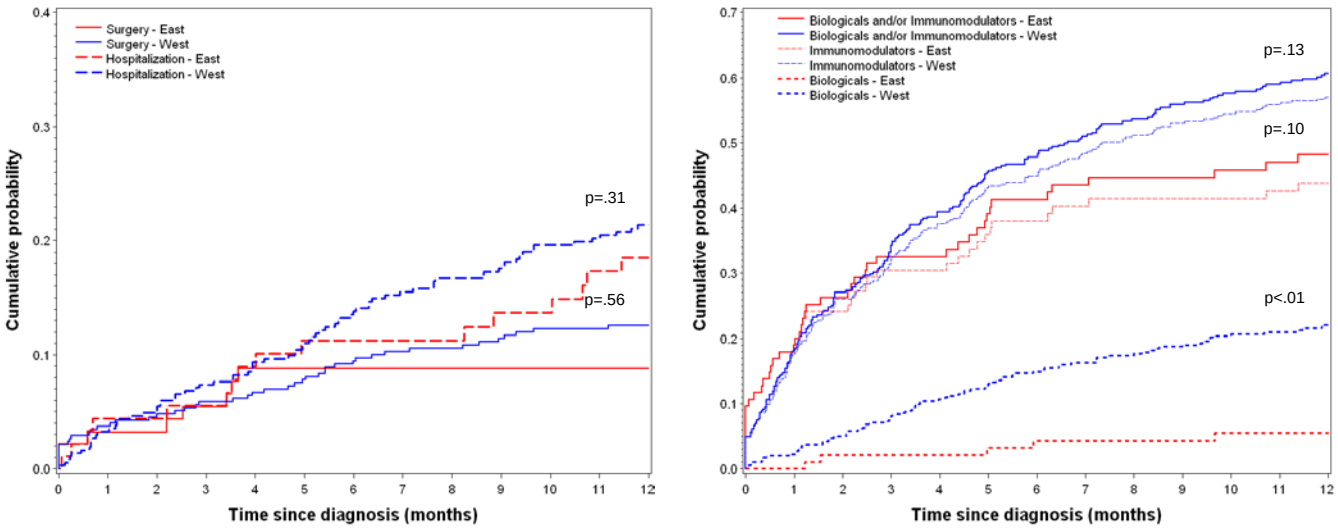


Figure 7. Cumulative probabilities for needing immunomodulators, hospitalization and surgery for Crohn's disease patients during the first year of disease.

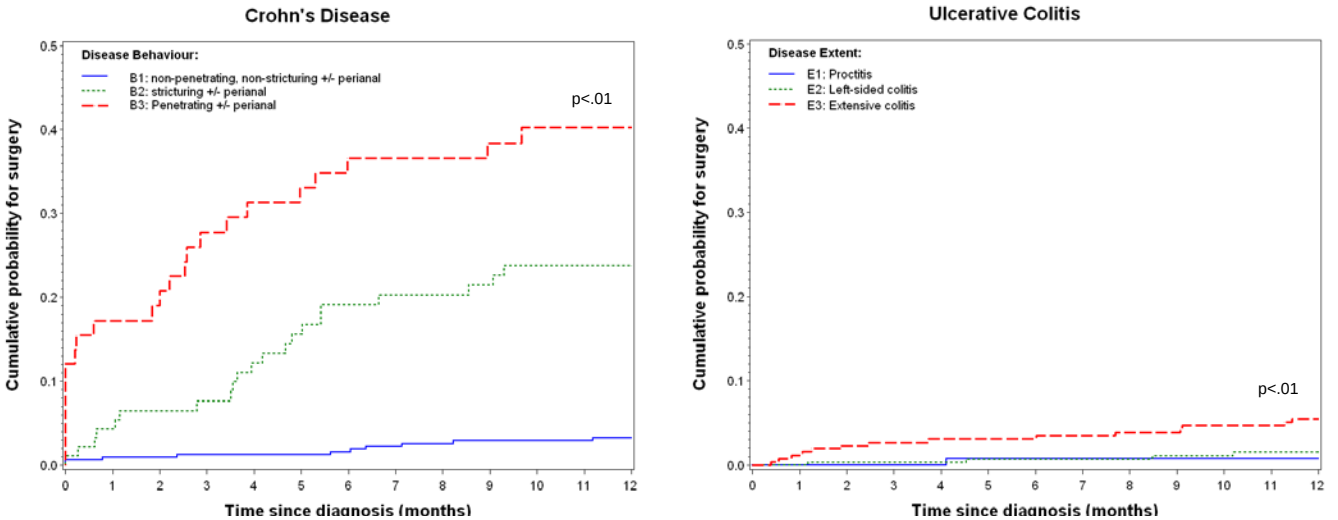


Figure 8. Cumulative probability for surgery during the first year of disease. IBD patients having a more aggressive inflammation burden, i.e. CD patients with penetrating or stricturing behaviour or UC patients with extensive disease, were more likely to require surgery.

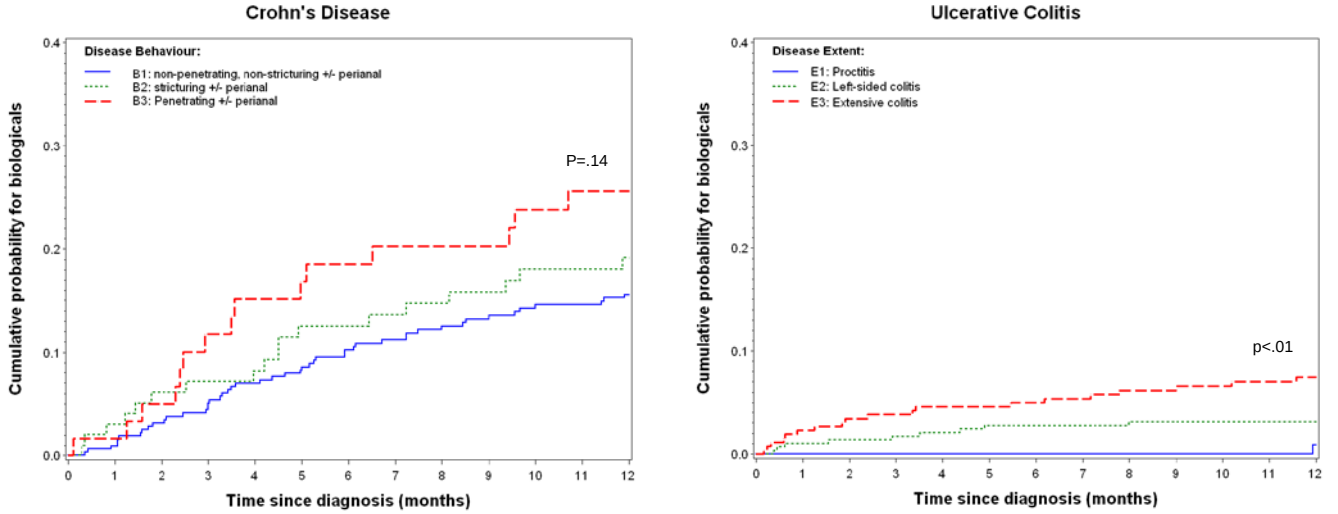


Figure 9. Cumulative probability for biological therapy during the first year of disease. UC patients with more extensive disease were more likely to require treatment with biologicals

Table 7. Resource costs (Euro) per patient in the first year of follow-up of 1,367 incident patients with inflammatory bowel disease.

Region	Diagnostics			Standard Medication[a]			Biological Therapy			Surgery		
	All sites	Western Europe	Eastern Europe	All sites	Western Europe	Eastern Europe	All sites	Western Europe	Eastern Europe	All sites	Western Europe	Eastern Europe
Crohn's disease												
Patients	502	400	102	465	370	95	82	77	5	85	74	11
Cost, mean (SD)	1,141	1,110	1,264	291	282	324	7,227	7,073	9,607	13,978	13,144[b]	19,586[b]
	(782)	(717)	(992)	(445)	(486)	(222)	(4,321)	(4,366)	(2,875)	(6,921)	(6,419)	(7,862)
Ulcerative colitis												
Patients	709	561	148	647	507	140	30	29	1	19	17	2
Cost, mean (SD)	662	642[b]	740[b]	577	594	513	4,924	5,034	1,729	18,510	19,039	14,014
	(270)	(238)	(355)	(709)	(737)	(593)	(3,838)	(3,857)	(0)	(7,630)	(7,916)	(0)
IBD unclassified												
Patients	147	141	6	134	128	6	11	11	0	6	6	0
Cost, mean (SD)	789	790	766	397	402	297	5,713	5,713	0	13,214	13,214	0
	(455)	(455)	(516)	(398)	(406)	(105)	(3,813)	(3,813)	(0)	(1,960)	(1,960)	(0)

[a] All medications for IBD except infliximab and adalimumab

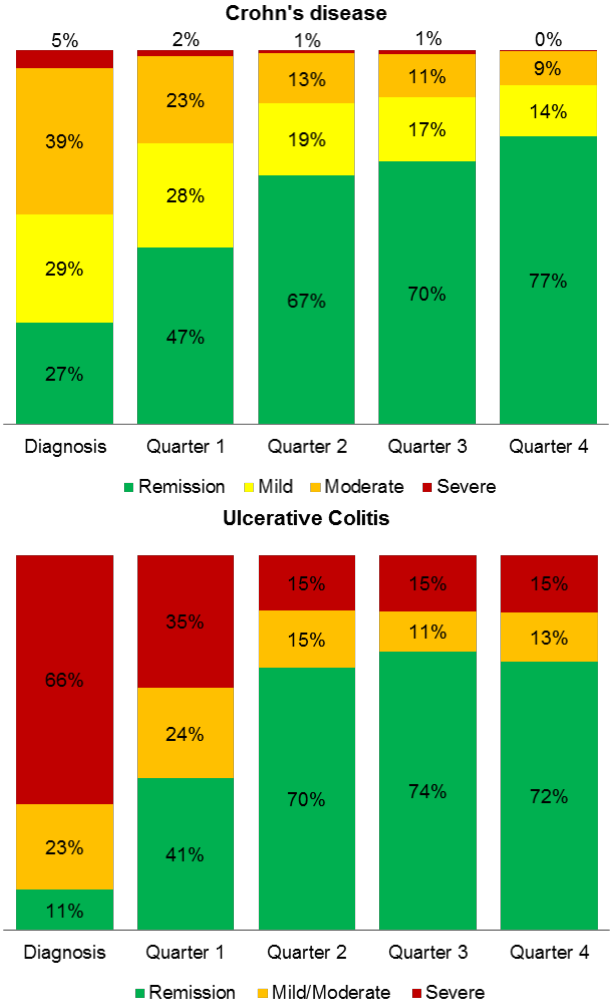


Figure 10. Distribution of disease activity during the first year of disease shows that the majority of IBD patients after 1 year of therapy experienced an indolent course with inactive to moderately active disease.

dian time to hospitalization: 3.6 months (range: 0-14)) and 12 (8%) in Eastern Europe (median time to hospitalization: 2.4 months (range: 0-15)) (p=0.01). All IBDU patients came from Western Europe (median time to hospitalization: 5.6 months (range: 0-10)). Disease behaviour, but not extent, was found to be associated with the risk of hospitalization (B2 vs. B1: HR 2.9, 95% CI: 1.8-4.9; B3 vs. B1: 5.2, 95% CI: 3.0-9.1; p<0.001).

4.4.4 The use of biological therapy in Eastern Europe is limited

Biological agents were administered to a total of 93 (18%) CD patients (infliximab n=66, 71%; adalimumab n=27, 29%). Significantly more CD patients in Western Europe (n=87; 21%) received biological therapy than in Eastern Europe (n=6; 6%) (Figure 7). In UC, 32 (5%) patients were administered biological therapy (only infliximab). As for CD, significantly more Western European UC patients (n=31; 6%) were treated than in Eastern Europe (n=1; 1%), p<0.01. Twelve (8%) Western European IBDU patients received biologicals. Most patients received biological therapy because of refractoriness to other treatments or steroid dependency and no difference in indications were found between geographic regions or types of diagnosis. The probability of needing biological therapy was highest for CD (CD vs. UC: HR 2.3, 95% CI: 1.4-3.6; p<0.01). No association between smoking status and disease classification with the risk of biological therapy was found in the cox-analysis in CD or UC patients (Figure 9).

4.4.5 Disease activity improved during follow-up

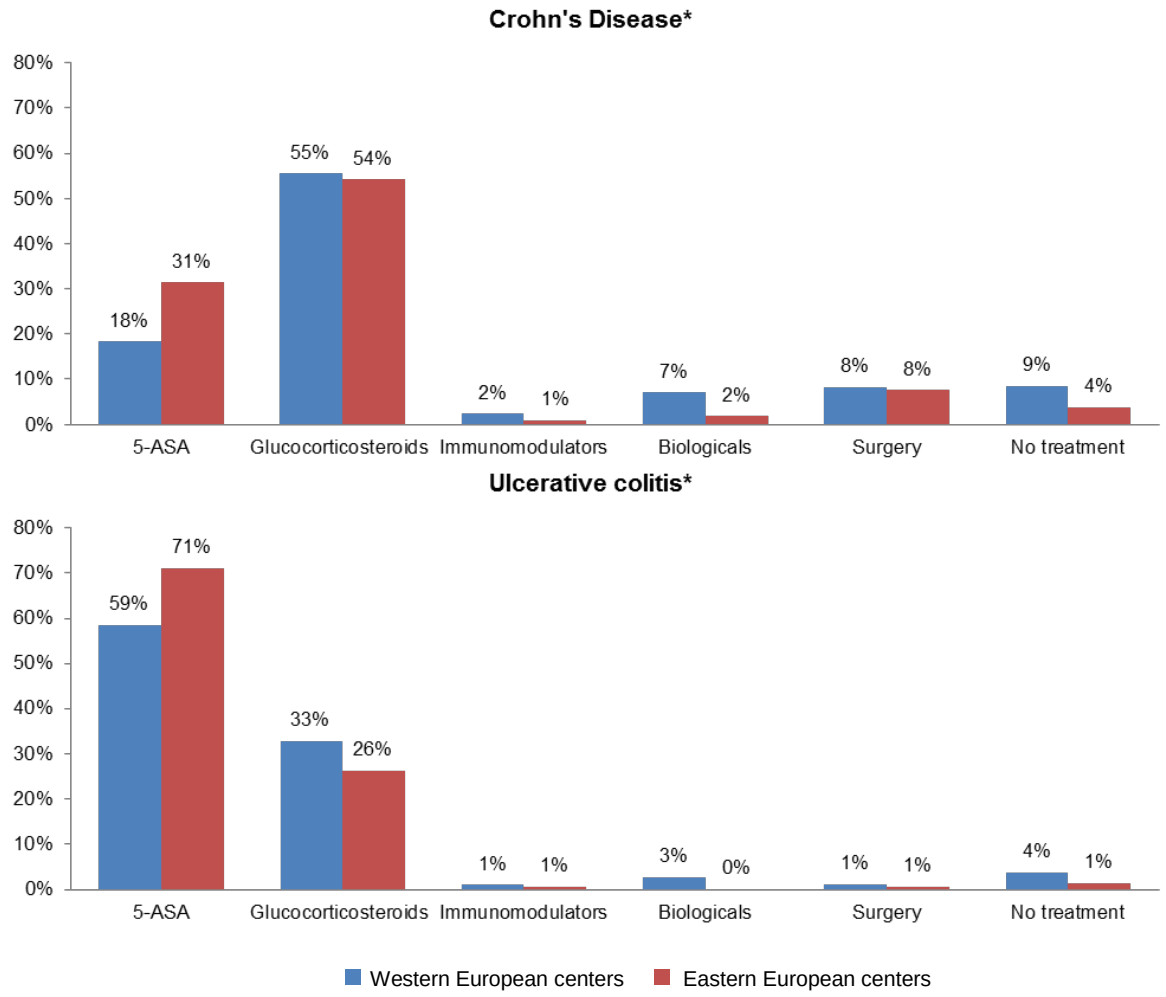
A subgroup of 328 (64%) CD patients and 448 (63%) UC patients had available data on disease activity during follow-up. The proportion of patients in remission increased from 11% in UC and 27% in CD at time of diagnosis to 71% and 77%, respectively, at one year follow-up (Figure 10). This observation was true for both geographic regions separately (data not shown). The majority of UC patients in remission at one-year follow-up had received 5-ASA (n=178; 61%) or GCS (n=68; 23%) as their highest treatment step, while 28 (10%) had received immunomodulators, 12 (4%) received biological therapy and five (2%) patients had a colectomy. For CD patients most patients had received immunomodulators (n=80; 32%) or GCS (n=60; 24%) as their highest treatment step, while 34 (13%) were treated with 5-ASA, 33 (13%) with biologicals and 41 (16%) had a resection.

4.4.6 Death

Eight patients died during follow-up (0.6%, five CD, two UC, one IBDU) a median time of nine months (range: 2-14) after diagnosis. Patients came from Western Europe only. Two UC patients had left-sided colitis, three CD patients had colonic and two CD patients ileocolonic localization. Two CD patients died due to sepsis after IBD surgery, while six patients died of non-IBD related causes.

4.4.7 Cancer

Six patients (0.4%, 2 CD and 4 UC; 1 UC patient from Eastern Europe; diagnostic delay: 1.6 mo. (range: 0-5 yr.)) were diagnosed with cancer, a median time of two months after IBD diagnosis



*difference between geographic regions p<0.05

Figure 11. Initial treatment (mono and combo therapy) during the first three months of disease in Eastern and Western European centres shows that 5-ASA is the first choice of treatment in UC vs. steroids in CD.

	SIBDQ		SF-12, MCS		SF-12, PCS	
	CD	UC	CD	UC	CD	UC
Coming from Eastern Europe	-	-	p=0.049	-	-	-
Age < 40 yr at diagnosis	-	-	-	-	-	p=0.032
Being a non-smoker	-	p<0.001	-	-	-	-
Having an education	-	-	-	-	p<0.001	-
No extra-intestinal manifestations	-	-	-	-	p=0.045	-
No biological therapy during follow-up	-	p<0.001	p=0.037	p<0.001	-	-
Shorter disease extent in UC	-	P=0.025	-	-	-	-

PCS, physical component summary score; MCS, mental component summary score

Table 8. Factors influencing positive changes in health-related quality of life at follow-up.

(range: 0-14).. One UC patient with extensive colitis had colon cancer diagnosed simultaneously with the IBD diagnosis, while the remaining patients had extra-intestinal cancer. Three of four UC patients had extensive disease and one had left-sided colitis, while one CD patient had L2 and one had L1 localization. One CD patient received azathioprine prior to the cancer diagnosis.

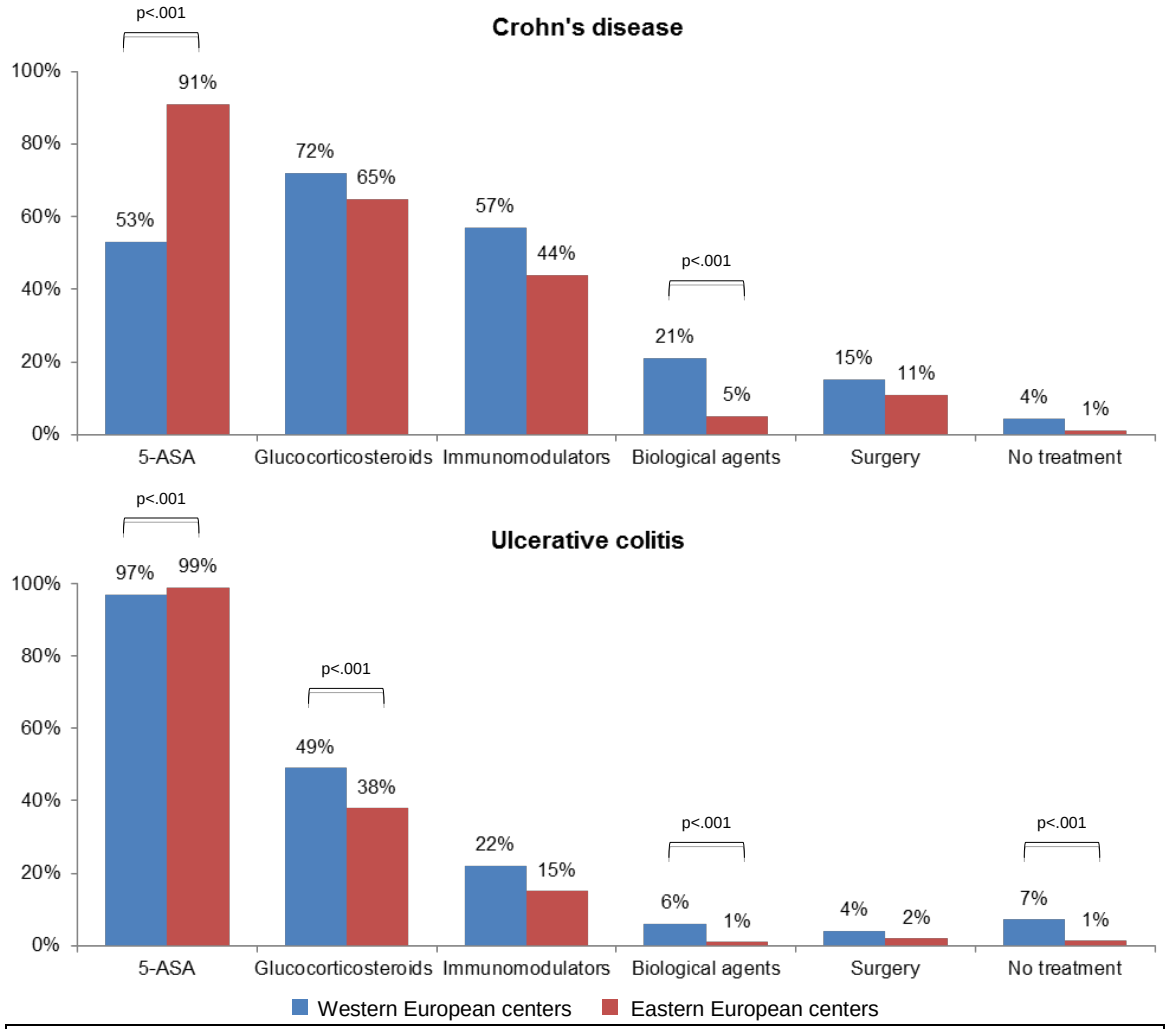
4.5 THE USE OF 5-ASA IS MORE COMMON IN EASTERN EUROPE WHILE VERY FEW PATIENTS RECEIVE BIOLOGICAL AGENTS

4.5.1 Initial treatment and treatment choices during the initial year of disease

Choices of initial treatment were assessed within 1,408 (93%) patients from the original cohort, as the centre from Pirkanmaa, Finland, due to local restrictions, had insufficient data regarding induction therapy and was excluded from this analysis. Choices of treatment within the follow-up period were assessed within the follow-up cohort. The initial treatment in Western and Eastern European centres during the first three months of disease is shown in Figure 11 while the cumulative probabilities for treatment steps within 12±3 months of follow-up are shown in Figure 12. Overall, regional differences were noted: more Eastern European CD and UC patients were treated with 5-ASA and significantly more Western European patients received biological therapy. This observation was confirmed when analysing the distribution of CD and UC patients within the six treatment steps during the follow-up period (Figures 13 and 14).

4.5.2 Crohn's disease patients on 5-ASA mono-therapy

A subset of 105 (21%) CD patients in the follow-up cohort only received 5-ASA as initial treatment (Western Europe: 77 (19%),



	CD		UC	
Median time to treatment	**Western Europe**	**Eastern Europe**	**Western Europe**	**Eastern Europe**
5-ASA	1 d. (-6-12 mo.)	0 d (-1-11 mo.)	0 d. (-7-12 mo.)	0 d. (0-2 mo.)
Glucocorticosteroids	1 d. (-4-12 mo.)	0 d. (-1-11 mo.)	1 d. (-4-12 mo.)	3 d. (0-10 mo.)
Immunomodulators	2 mo. (-2-12 mo.)	1 mo. (0-11 mo.)	4 mo. (0-12 mo.)	3 mo. (1-12 mo.)
Biological agents	5 mo. (0-15 mo.)	6 mo. (1-13 mo.)	3 mo. (0-15 mo.)	12 mo.
Surgery	3 mo. (-2-15 mo.)	1 mo. (0-15 mo.)	5 mo. (0-14 mo.)	6 mo. (1-11 mo.)

Figure 12. Cumulative probabilities for treatment steps during the first year of disease in a European inception cohort. Significant more patients in Western Europe received biological agents, while more patients in Eastern Europe received 5-ASA treatment

Table 9. Environmental factors and inflammatory bowel disease patients' subsequent risk (Odds ratio, 95% CI) of hospitalization, surgery, biological therapy, severe disease course, extra-intestinal manifestations, and disease classification in a European inception cohort.

	Hospitalization	Surgery	Biological therapy	Severe disease course	Extra-intestinal Manifestations	Disease behaviour
			Crohn's disease			
Age at diagnosis, per year	-	-	0.98 (0.96-1.0)	0.97 (0.96-0.99)	-	-
Being Eastern European	-	-	0.11 (0.03-0.36)	0.33 (0.19-0.58)	-	-
Current smoking	-	-	-	-	-	1.59 (1.03-2.44)
High intake of caffeine	-	2.18 (1.01-4.71)	-	1.86 (1.15-2.99)	-	-
Appendectomy	-	-	0.25 (0.07-0.83)	0.34 (0.17-0.66)	-	-
High daily sugar intake	-	-	-	0.53 (0.33-0.86)	-	-
Breastfeeding during infancy	-	-	-	-	2.34 (1.17-4.67)	-
Ulcerative colitis	**Hospitalization**	**Surgery**	**Biological therapy**	**Severe disease course**	**Extra-intestinal manifestations**	**Disease extent**
Age at diagnosis, per year	0.98 (0.96-1.0)	-	0.95 (0.92-1.0)	0.99 (0.98-1.0)	-	-
Female vs. male	-	-	-	-	2.14 (1.25-3.68)	0.68 (0.49-0.95)
Being Eastern European	0.31 (0.14-0.69)	-	0.08 (0.01-0.62)	0.55 (0.36-0.84)	-	-
IBD in 1st degree relatives	0.29 (0.09-0.95)	-	-	-	2.22 (1.10-4.51)	1.76 (1.07-2.89)
Never smoked	-	-	2.86 (1.21-6.75)	-	-	-
Oral contraceptive	-	-	-	-	-	0.56 (0.33-0.98)
Daily fast food intake	-	5.78 (1.88-17.76)	-	-	-	2.03 (1.17-3.52)
High intake of caffeine	-	-	-	-	2.86 (1.55-5.26)	-

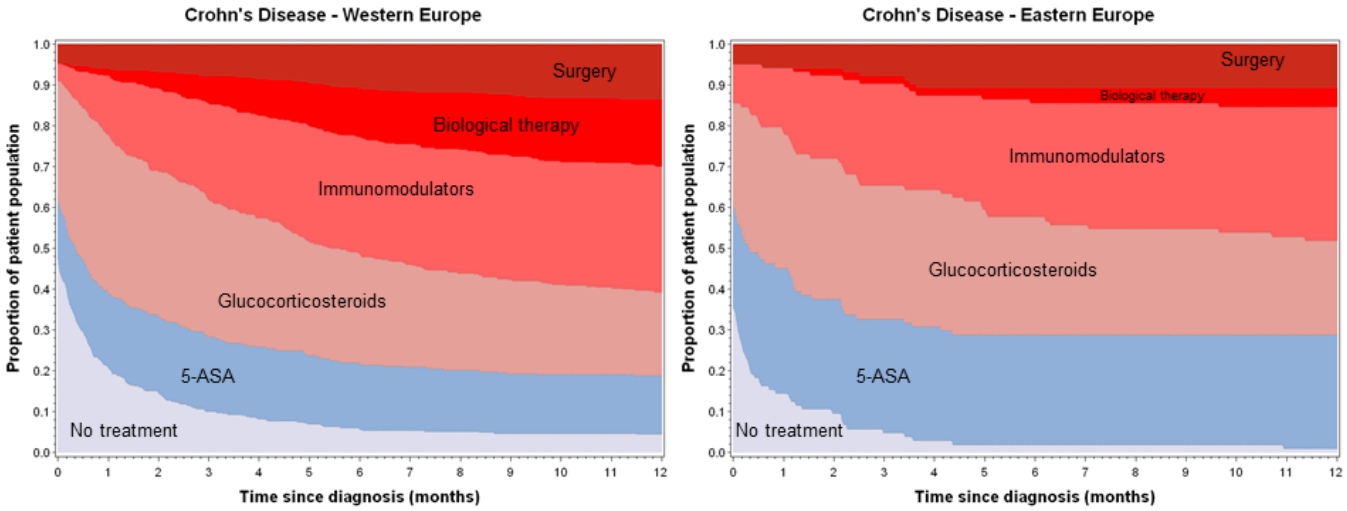


Figure 13. Distribution of Crohn's disease patients within treatment steps during the first year of disease in Western and Eastern Europe

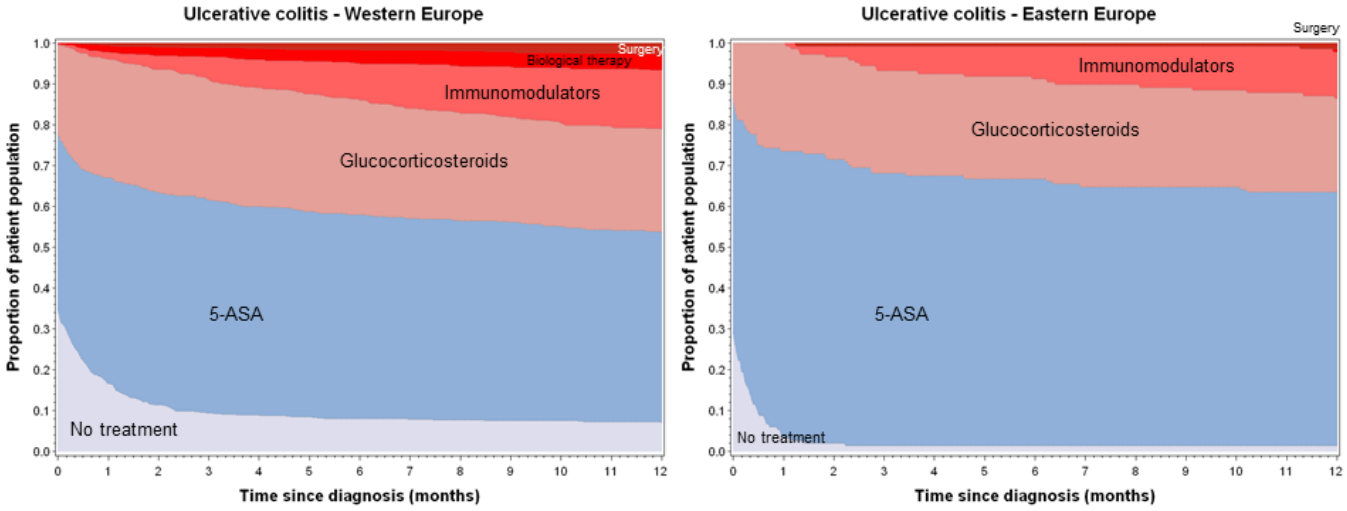


Figure 14. Distribution of ulcerative colitis patients within treatment steps during the first year of disease in Western and Eastern Europe

Eastern Europe: 28 (27%), p=0.08). During follow-up the majority of patients (49 (64%) in Western Europe and 27 (96%) in Eastern Europe) remained on 5-ASA mono therapy. More patients had non-penetrating, non-stricturing disease (44 (90%) in Western Europe, p<0.01, and 21 (78%) in Eastern Europe, p=0.66) compared to patients not treated with 5-ASA mono therapy only during follow-up while disease location did not differ (data not shown). In Western Europe 12 (16%) received GCS, 11 (14%) received immunomodulators, three (4%) received biological agents and two (3%) underwent surgery. However, 49 (64%) did not progress up the treatment pyramid. In Eastern Europe only one (4%) patient stepped up to GCS, while 28 (96%) remained on 5-ASA.

4.6 MORE RESOURCES ARE SPENT ON DIAGNOSING EASTERN EUROPEAN IBD PATIENTS – RESOURCE UTILIZATION AND COSTS DURING THE INITIAL YEAR OF DISEASE

The total expenditure on the 1,367 patients in the study was € 4,142,488 in the first 12 months following diagnosis, with € 1,158,636 (28%) spent on diagnostic procedures, € 561,558 (14%) on standard medication, € 803,183 (19%) on biological therapy, and € 1,619,111 (39%) on surgery, Figure 15. CD patients accounted for € 592,628 (74%) of the costs for biological therapy and € 1,188,132 of surgery costs. Total costs were highest in Western Europe for UC (Western Europe: € 1,131,032; Eastern Europe: € 211,180), CD (Western Europe: € 2,065,629; Eastern Europe: € 423,262), and IBDU (Western Europe: € 305,005; Eastern Europe: € 6,379). However, the expenditure per patient for most categories of resource utilization was greater in Eastern Europe as compared to Western Europe (Table 7). The differences between Eastern and Western Europe for diagnostics in UC and surgery in CD were found to be statistically significant.

When further analysing the diagnostic procedures in the follow-up cohort, differences between Western and Eastern Europe were noted if the number of patients who, in addition to a colonoscopy, also had a sigmoidoscopy (CD: 18 (4%) vs. 3 (3%); UC: 37 (7%) vs. 20 (14%)) or bowel x-ray (CD: 40 (10%) vs. 12 (2%); UC: 15 (14%) vs. 19 (13%)) as part of their diagnostic work-up. Furthermore, of CD patients who had an MRI, in Western Europe 27 (7%) also had a CT and 7 (2%) a capsule endoscopy, while in Eastern Europe 8 (8%) patients had a capsule endoscopy. No UC patients had additional investigations to MRI performed. Biological therapy accounted for 13% of UC, 26% of CD and 21% of IBDU expenditure in Western Europe, and 1% of UC, 11% of CD and 0% of IBDU expenditure in Eastern Europe. Independent predictors of cost were the type of diagnosis and the type of resource (treatment)

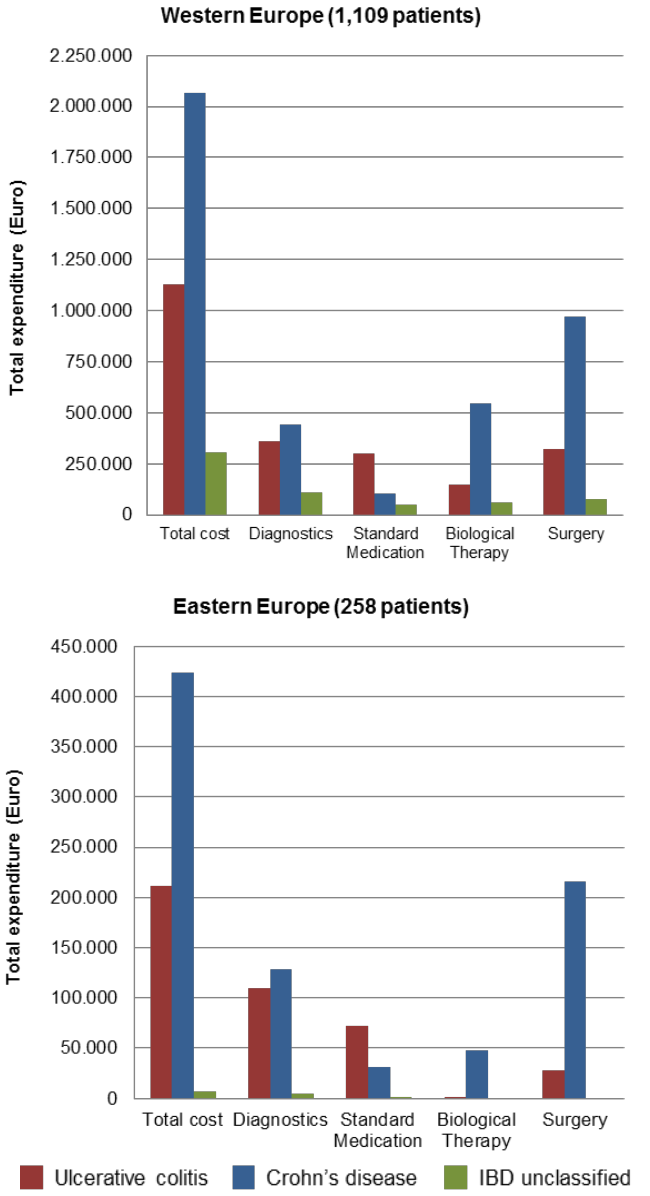


Figure 15. Total expenditures in the 2010 European inception cohort of 1,367 patients with IBD during the first year following diagnosis. Total costs for all types of disease were higher in Western than in Eastern Europe (UC: € 1,131,032 vs. € 211,180; CD: € 2,065,629 vs. € 423,262); IBDU: € 305,005 vs. € 6,379).

used with the patients, as well as various combinations of region and resource, resource and diagnosis, and finally region with resource with diagnosis (p<0.01). The distribution of the cumulated expenses during the first year of disease for CD and UC patients are shown in Figures 16 and 17.

4.7 GENERIC AND DISEASE-SPECIFIC QUALITY OF LIFE IMPROVED DURING FOLLOW-UP

HRQoL was assessed in 1,079 adult IBD patients (71% of the original cohort), 402 (37%) with CD, 575 (53%) with UC, and 102 (10%) with IBDU (Appendix). A subset of 436 (31%) patients from the original cohort did not give consent to answer the questionnaires (288, 64%) or were lost during follow-up (148, 34%) and thus were excluded. Patient characteristics only differed from the original cohort in that a higher proportion CD patients and a smaller proportion of IBDU patients were recorded.

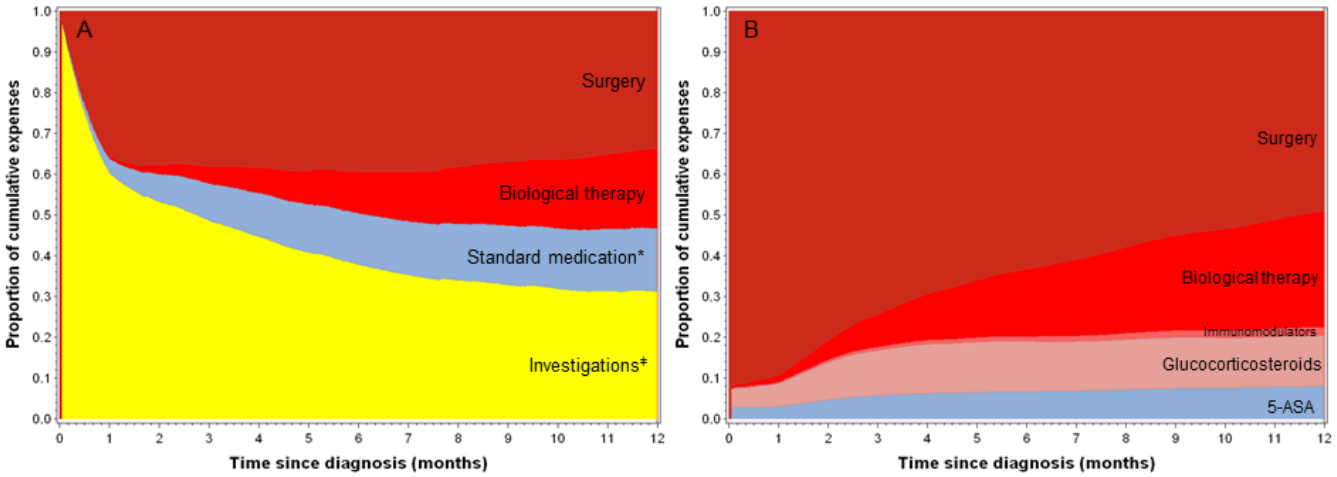
No regional difference in generic or disease-specific HRQoL was found at diagnosis or at follow-up for CD and IBDU patients. In UC, Western European patients had a significantly higher mean SIBDQ score at diagnosis (48.8 vs. 44.9, p<0.01) and PCS (46.9 vs. 44.3, p=0.02) but not at follow-up (details regarding HRQoL scores are described in paper IV). SIBDQ scores improved significantly during follow-up in all CD patients (Western Europe: 44.9 to 53.6; Eastern Europe: 45.3 to 55.3; p<0.01), in all UC patients (Western Europe: 48.8 to 55.7; Eastern Europe: 44.9 to 57.4; p<0.01), and in Western European IBD patients only (49.9 to 54.9; p=0.01). As shown in Figure 18 the proportion of patients with good HRQoL (SIBDQ total score > 50) improved in all but Eastern European IBDU patients. Mean SIBDQ scores for all IBD patients improved to being 'good' in the majority of centres (p<0.01) (Figure 19).

Similarly, CD and UC patients from both regions improved in both SF-12 summary scores, while improvements were only seen in Western European IBDU patients for the MCS summary score (p<0.01) (Figure 20). Only Eastern European UC and IBDU patients achieved a generic equal to or higher than the healthy background population. For UC patients, limited disease extent (E1 vs. E2: OR 5.3 CI95% 2.0-14.1; E1 vs. E3: OR 4.9 CI95% 1.8-13.8; p<0.01), not receiving biological therapy (no biologicals vs. biologicals: OR 25.2 CI95% 2.4-259.8, p<0.01), and not undergoing surgery during follow-up (no surgery vs. surgery: OR 4.4 CI95% 1.1-18.7, p=0.03) was associated with improving SIBDQ scores during follow-up. No significant predicting factors for CD patients were found. Factors influencing improvements in disease-specific and generic HRQoL are outlined in Table 8.

4.8 MORE EASTERN EUROPEAN IBD PATIENTS ARE EXPOSED TO DIETARY RISK FACTORS OF IBD

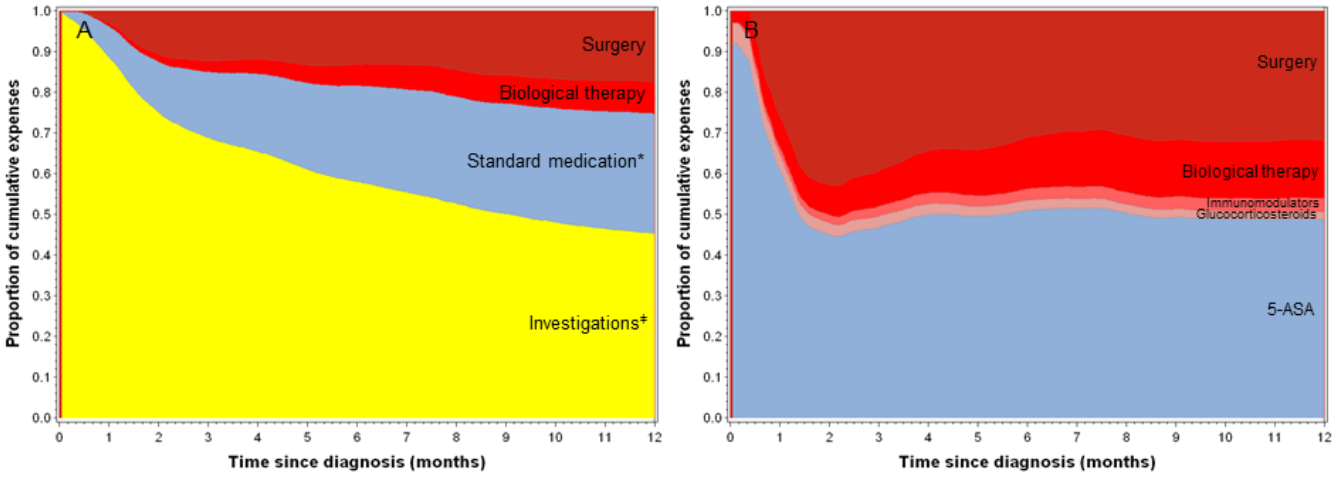
The environmental factors questionnaire was answered by 1,182 adult IBD patients (76% of the original cohort), 444 (38%) had CD, 627 (53%) had UC, and 111 (9%) had IBDU. A total of 333 patients did not answer the questionnaire because of non-consent (56%) or being lost during follow-up (44%). These patients differed only in the distribution of diagnosis (the fraction of CD patients was larger and the fraction of IBDU patients smaller compared to responders), and in terms of extra-intestinal manifestations (fewer patients had extra-intestinal manifestations compared to responders).

Significant differences between Eastern and Western European patients were observed regarding exposure to environmental factors prior to IBD diagnosis. More CD and UC patients in Eastern Europe had received vaccinations against several agents (tuberculosis, pertussis, measles, rubella, diphtheria, and polio; p<0.01) and more Western European patients had experienced infections (measles, pertussis, and mumps) during childhood (p<0.01). The frequency of appendectomy before the age of 20 was higher in Western European UC patients (p<0.01). Regarding dietary habits both CD and UC patients in Eastern Europe reported a higher daily consumption of sugar and lower consumption of fibres (p<0.01). Furthermore, more UC patients in Eastern Europe had a daily intake of fast food, while more Western European CD patients reported daily consumption of fruit and vegetables (p<0.01) (Figure 21). However, no regional differences were found in smoking habits, use of oral contraceptives or caffeine intake. For a full description of all investigated factors please refer to paper V. Environmental factors predicting initial disease presentation and outcomes are outlined in Table 9.



* Standard medication: 5-ASA, glucocorticosteroids, and immunomodulators
‡ Investigations: diagnostic procedures and investigations during the first year from diagnosis

Figure 16. Distribution of cumulative expenses for Crohn's disease patients regarding A) treatment and investigations and B) treatment choices during the first year from diagnosis in a European inception cohort



* Standard medication: 5-ASA, glucocorticosteroids, and immunomodulators
‡ Investigations: diagnostic procedures and investigations during the first year from diagnosis

Figure 17. Distribution of cumulative expenses for ulcerative colitis patients regarding A) treatment and investigations and B) treatment choices during the first year from diagnosis in a European inception cohort

4.9 QUALITY OF CARE DIFFERS IN EUROPE REGARDING INFORMATION ABOUT IBD AND PATIENT EDUCATION

Quality of care assessment was available from 947 patients (62% of the original cohort; 148 were missing because of being lost during follow-up, 420 did not give consent), 363 (38%) with CD, 485 (51%) with UC, and 99 (10%) with IBDU (Appendix). The questionnaire was answered a median time interval of 14 months after inclusion (range: 0-24 months). Eastern and Western European patients did not differ in terms of general knowledge about IBD before diagnosis as only one in four patients reported having any knowledge. In both geographical regions information regarding IBD was mainly found on the internet by IBD patients, while the main source of IBD information in the health care system was the hospital doctor. However, more IBD patients in Eastern Europe reported having sought out information on their own, and more patients used the internet as their source of information compared to those in Western Europe. A greater proportion of patients in Eastern Europe than in Western Europe had received disease-related education. In Eastern Europe the IBD specialist was the only source of disease-related education, in contrast to Western Europe where IBD nurses took part in patient education alongside the IBD specialist. For further details please refer to paper VII. Despite the regional differences observed the proportion of patients reporting good overall satisfaction with their level of information was similar in Eastern and Western Europe.

5. DISCUSSION

The present thesis constitutes a comprehensive description of the disease course and management of European IBD patients in their first year after diagnosis. It is the result of a unique collaboration of highly committed researchers from Eastern and Western Europe, who with limited funding and manpower succeeded in creating a new European population-based and web-based inception cohort.

5.1 WEB-BASED EPIDEMIOLOGY

Epidemiological studies are cumbersome to perform and multicentre studies involving multiple countries are made difficult or sometimes prohibited outright by local data legislations. An essential aim of this project was to create a database that was

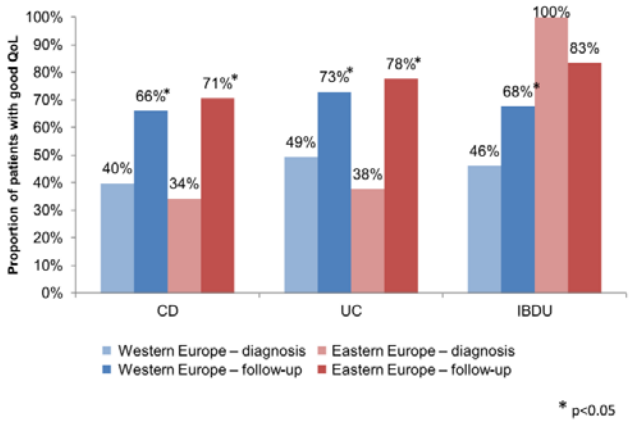


Figure 18. Proportion of patients with good disease-specific health-related quality of life (SIBDQ score >50) at diagnosis and follow-up in an unselected IBD cohort. Quality of life improved in the majority of CD and UC patients in both Eastern and Western Europe.

secure and that fulfilled the requirements for secure centralised data storage as well as data sharing across borders, and that was also web-based, thereby making remote input and access of data possible. This web-based approach was chosen because of the experiences from the EC-IBD cohort study[32], where centres sent data on paper forms by mail to a centralized unit for data collection or used a partly web-based approach[59].

In this study, participants were involved in all steps of the database construction to familiarize them with the database and to try to create a feeling of ownership in the group. However, academic databases such as the DCCD[11,30] or the French EPIMAD registry[62] are limited in their applicability during daily clinical work by the fact that they are time-consuming to use, because of the large amount of data that require collecting. This was also the case for the EpiCom database[34], as time consumption remained an important concern for most participants. Another criticism is that the EpiCom database was only available in the English and Russian languages for the study, which may have caused interpretative problems in the centres if not all physicians and nurses involved had the relevant language skills.

5.2 INCIDENCE GRADIENT IN EUROPE – WERE ALL INCIDENT PATIENTS FOUND?

Only a few centres had organized prospective population-based inception cohorts before participating in the present study, most of them as part of the EC-IBD study[21,32,63]. However, primary catchment areas were required to be well-defined and all gastroenterology departments, gastroenterologists and general practitioners within the catchment areas to be contacted during the inclusion period. This was done in order to secure complete prospective inclusion of incident IBD patients with a diagnosis in 2010 and thereby to create a truly population-based cohort. Physicians and nurses were trained in the methodology of the study at several study group meetings prior to and during the inclusion period, to secure protocol adherence. Data quality and validity were secured by standardizing the criteria for case definition, methods of case ascertainment, time period of inclusion, the recorded clinical data, and follow-up intervals. Random audit visits and in-built data control in the database further contributed to the quality of the cohort.

Given the aforementioned initiatives the number of cases missed in the EpiCom cohort is assumed to be small and the observed annual incidence rates to be valid. This assumption is substantiated by the fact that most centres that previously had reported incidence numbers from their catchment area,– Croatia[64,65], Denmark[11,32,66], Estonia[67], Faroe Islands[68], Finland[69], Greece[32], Hungary[21], Iceland[15], Israel[32], Italy[32,70,71], Romania[72], and Spain[32] – all found comparable or even higher incidence rates for CD and UC in this present study[73]. Of note, the combined incidence rate of IBD observed on the Faroe Islands (81.5 per 100.000) is the highest rate to be reported to this day. In 1981-1988 annual incidence rates were found to be 23.9 per 100.000[68], while in 2005-2009 they were 35.5 per 100.000 on the Faroe Islands[74]. This steep increase in IBD occurrence is partly explained by methodological differences compared to the present study, since the one from 2005-2009 was retrospective and registry-based. In a current validation cohort with patients diagnosed in 2011 and in 2012 within the EpiCom collaboration the reported incidence rates on the Faroe Islands are similar to the high rate reported here (personal communication, K.R. Nielsen). Furthermore, diagnostic procedures and diagnostic delay on the Faroe Islands were similar to other Western European countries.

Overall, the occurrence of both CD and UC was found to be twice as high in Western Europe compared to Eastern Europe (CD: 6.3/100,000 vs. 3.3/100,000; UC: 9.8/100,000 vs. 4.6/100,000). This is a larger gradient than the North-South gradient found in the EC-IBD study, where rates for CD were 40%, and for UC were 80%, higher in Northern Europe than in Southern Europe. Only Hungary, where increasing incidences have been

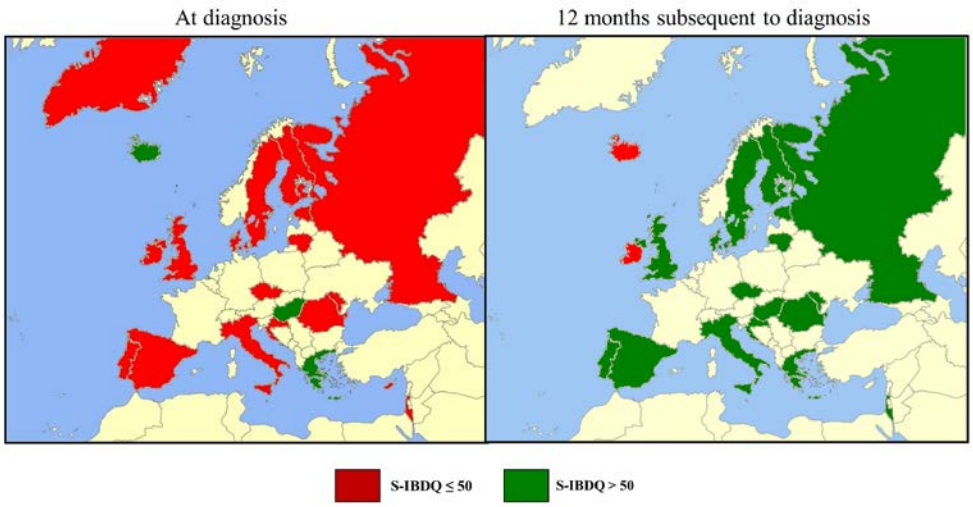


Figure 19. Mean Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores in the 2010 IBD inception cohort at diagnosis and 1 year FU in Eastern and Western Europe. During the first year subsequent to diagnosis - and due to IBD-specific medical and surgical treatments - the overall SIBDQ score was good in almost all centres.

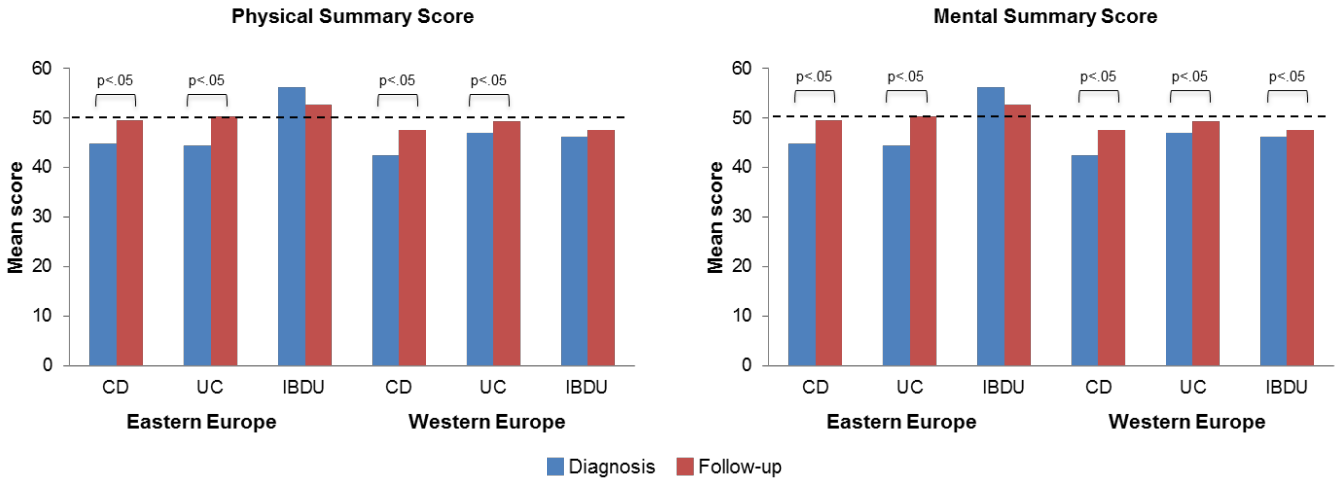


Figure 20. Mean summary scores for the Short Form 12 questionnaire at diagnosis and follow-up in Crohn's disease (CD) and ulcerative colitis (UC) patients. All patients improved their generic quality of life scores, however only Eastern European UC patients had scores comparable to the healthy background population at follow-up.

reported previously and which is one of the wealthier Eastern European countries i n terms of GDP, found incidence rates for IBD comparable to Western European centres. The incidence rates observed in this study were, as in the EC-IBD study[32], subject to great variation both between and within regions. This has been noted previously in comprehensive reviews[75,76] where, however, differences in methodology and observation period in the studies likely contributed to the variation. Because of the standardisation of methods and inclusion period in this study we were able to perform a direct comparison of incidence rates in Europe. Diagnostic procedures used in the participating centres were, overall, not significantly different and since the diagnostic delay was short and comparable across Eastern and Western Europe it seems unlikely that the incidence rates observed were biased by an accumulation of undetected cases. It is therefore more likely that the variation observed in IBD incidence reflects variation in environmental and dietary risk factors for the diseases[77].

5.3 DIFFERENCES IN ENVIRONMENTAL FACTORS BETWEEN EASTERN AND WESTERN EUROPE

The impact of environmental factors on the risk of IBD remains uncertain due to inconsistent findings in studies as well as methodological limitations (e.g. the lack of prospective studies) in the assessment of environmental factors, e.g. the large number of possible influencing factors, recall bias and possible changes in diet because of symptoms before the IBD diagnosis[75,78]. Given the recent increases in CD and UC incidence observed in previously low-incidence regions such as Eastern Europe it follows that changes in the environment, such as a Westernisation of lifestyle including dietary habits, are responsible for these increases[26,77].

In this study we observed that Eastern European CD and UC patients reported higher frequencies of dietary risk factors prior to being diagnosed with IBD[79]. IBD patients from Eastern Europe had low daily fibre intake as well as high daily sugar consumption, and more Eastern European than Western European patients reported daily consumption of fast food among those with UC but not CD. High consumption of dietary fibre, especially fruit and vegetables[80], has been shown to decrease the risk of CD[54,80,81] and UC[54] while a high daily sugar consumption is associated with a higher risk of IBD[51,54,82,83]. A previous study has reported an increased risk of IBD associated with frequent fast-food consumption[84]. But the question remains whether these dietary habits, e.g. high sugar intake, are causing the disease or are a consequence of IBD symptoms with patients simply trying to counteract weight loss or fatigue[85]. Furthermore, childhood infections and vaccinations constitute a further potential risk factor since a lack of exposure to enteric pathogens during childhood is suspected to be a risk factor for CD especially[86,87] and that multiple childhood infections and poor hygiene are protective against IBD[88].

Regarding smoking status at diagnosis no differences were found between Eastern and Western Europe and in both regions more CD patients were active smokers and more UC patients were former smokers at diagnosis, in accordance with previous population-based cohorts[11,21,89]. Smoking, perhaps the most thoroughly investigated environmental risk factor, increases the risk for, and worsens the disease course of CD while being protective against UC[90], and these observations were confirmed in the present cohort based on clinical presentation at diagnosis and disease course. Likewise, the use of oral contraceptives did not differ between Eastern and Western Europe. The use of oral contraceptives has previously been associated with an increased risk of IBD[91] while its impact on disease course is uncertain[92,93]. We found that oral contraceptives decreased the risk of extensive UC at diagnosis as well as the need for more potent treatment steps during follow-up, in accordance with a Danish inception cohort study[94].

Overall, the differences observed in the distribution of environmental risk factors assessed in this study did not seem to explain the West-East gradient. The high occurrence of potential risk factors in Eastern European IBD patients seems to confirm the hypothesis of environmental factors being a key element in the emergence of IBD in Eastern Europe. However, since no control group was available for comparison in this study and because of the high risk of recall bias regarding childhood factors and diet prior to diagnosis these findings need further investigation and confirmation in controlled prospective studies.

5.4 DIFFERENCES IN CLINICAL PRESENTATION, DIAGNOSTIC PROCEDURES AND DIAGNOSTIC DELAY

Although we observed a marked difference in the occurrence of IBD in Europe as well as in the frequency of environmental risk factors, patient characteristics of CD and UC patients were similar in Eastern and Western Europe. Patients were more likely to be diagnosed in their mid-thirties, as with previous population-based

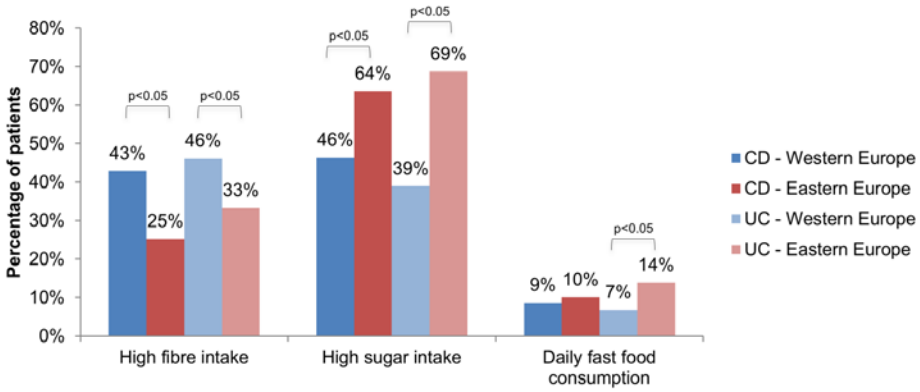


Figure 21. Frequency of selected environmental factors at diagnosis in European patients with inflammatory bowel disease showing that Eastern European patients reported a low-fibre, high-sugar and frequent fast-food diet.

cohorts[11–14,21,95,96]. A male predominance in both CD and UC was noted in both regions. This gender distribution differs from previous cohorts, which saw a female predominance in CD[11,13,14,18,95,97] while others have observed a male predominance in UC[12,14,15,21,96,97]. In accordance with the available literature, more CD than UC patients in both regions were current smokers at diagnosis, while more UC than CD patients were former smokers[98]. Finally, disease classification in both CD and UC patients did – like in the former EC-IBD study[97] –not differ between regions in this study and were similar to previous cohorts[11–14,21,95].

While access to some diagnostic procedures such as colonoscopy, capsule endoscopy or MRI may vary within geographical regions or countries, the diagnostic approach for obtaining an IBD diagnosis overall was very similar across the European centres. There were similar findings in the EC-IBD study of Northern and Southern Europe[97]. In the EpiCom study both regions acted in accordance with international guidelines[99–103], although the adherence to international guidelines is influenced by differences in practice across Europe as well as by socio-economic considerations. All CD, UC and IBDU patients had an endoscopy performed – almost 90% had a colonoscopy – as part of the diagnostic workup. Surprisingly, however, significantly more Eastern European UC patients had the recommended colonoscopy instead of a sigmoidoscopy performed compared to Western European UC patients, while no significant differences were found for CD and IBDU. Furthermore, the use of upper endoscopy was more pronounced in Eastern European CD and UC patients. Esophagogastroduodenoscopy is recommended in all paediatric and adolescent patients suspected of IBD[104,105], while this is only recommended in adult UC patients with upper gastrointestinal symptoms[99] or patients with IBDU but suspected of CD[100]. CD localization proximal to jejunum, however, occurred just as frequently in Western as in Eastern Europe (data not shown).

Interestingly, the median time from onset of symptoms to diagnosis (patient's and/or doctor's delay) was shorter in Eastern European than in Western European CD (3.4 months vs. 4.6 months) and UC (2.2 months vs. 2.5 months) patients. In a Danish population-based inception cohort the delay was 8.3 months for CD and 4.5 months for UC[11]. Improvements in, and increased availability of, new diagnostic tools in all of Europe might offer an explanation for this apparently shortened delay, e. g. 10% of Western European and 14% of Eastern European CD patients had a capsule endoscopy performed as part of their diagnostic procedures. On the other hand, it might be that awareness of IBD has increased due to the availability of information, especially via the internet and young patients researching their symptoms online earlier and seeking medical attention sooner[106].

5.5 EARLY TREATMENT WITH IMMUNOMODULATORS AND DIFFERENCES IN THE USE OF BIOLOGICAL THERAPY AND 5-ASA

Treatment of IBD in this cohort was more aggressive than in previous population-based cohorts[11,63,107–109]. Approximately 50% of CD and 20% of UC patients in both regions received treatment with immunomodulators at a very early stage within the first year subsequent to diagnosis. Immunomodulators have been used in IBD treatment of steroid-dependent patients[9,10] from the 1990s, thus explaining the infrequent use during the initial period after diagnosis in early cohorts[63,107–109]. Since then, the use of immunomodulators has increased both during follow-up of previous cohorts[63,107–109] as well as in more recent population-based inception cohorts from the previous decade[94,110], where 33% of CD and 10% of UC patients received immunomodulators during the first year. This trend of a 'top-down'[111] approach was continued in this cohort as physicians chose this line of treatment more rapidly and in more patients than observed previously. This rapid escalation of therapy might be the result of the "era of mucosal healing" as an important treatment goal[112].

Likewise, the use of biological therapy – available since 1998 in IBD treatment – during the first year of disease was greater than in previous inception cohorts[63,94,110]. However, significantly more CD and UC patients from Western Europe received biologicals. The introduction of biologicals was not significantly delayed in Eastern Europe[25], and therefore this observation is likely to be explained by differences between health systems across Europe. The majority of participating centres were IBD specialist centres, but differences in prescription restrictions and requirements before initiation of biological therapy might require a longer follow-up in this cohort in order to truly compare the geographical regions.

Very little is known about the treatment strategies in Eastern Europe, however it has previously been reported that 5-ASA is still widely used in CD maintenance[25]. Mono-therapy with 5-ASA was used for 21% of all CD patients in this cohort, with the majority of these patients remaining on 5-ASA mono-therapy throughout the observation time. Almost all Eastern European CD patients (91%) received treatment with 5-ASA during the first year of disease compared to approximately half of Western European CD patients (53%). For UC the cumulative probability was similarly high in Eastern and Western Europe; however 5-ASA treatment was initiated much earlier, within the first two months, in all Eastern European patients. Current guidelines do not recommend 5-ASA in the treatment of CD[10] as the efficacy of 5-ASA for inducing remission in CD patients in a recent meta-analysis could not be proven[113]. However, 5-ASA has been shown to be comparable to thiopurines in preventing clinical and surgical relapses in postoperative CD patients[114]. Additionally, in a Danish cohort, a mild

phenotype of 5-ASA-dependent CD patients benefited from long-term 5-ASA mono-therapy and had a lower cumulative probability of first intestinal surgery[115,116].

5.6 UNCHANGED DISEASE COURSE IN EUROPE

The differences observed in IBD management did not, however, impact on the initial disease course within the follow-up period, because comparable surgery and hospitalization rates in Eastern and Western Europe for CD patients and surgery rates for UC patients were found[117]. Only hospitalization rates in UC patients were found to be significantly higher in Western Europe. Overall, surgery rates for CD and UC patients have declined during the past decades[11,118–120] accompanied by the introduction of earlier and more aggressive IBD treatment with immunomodulators and biological therapy, an earlier diagnosis and thus a greater number of patients diagnosed with mild disease and a more conservative approach towards surgery by the physicians[121]. At the same time hospitalization rates have remained constant[119] or decreased[122] over time in North American population-based cohorts, but overall we have few data about hospitalization risk. One recent Canadian cohort study found hospitalization rates of 24% for CD[119] during the first year of disease and this is comparable to the rates in Western European patients in the EpiCom cohort.

Population-based cohorts of patients diagnosed after the introduction of biological agents from Western Europe and North American have reported surgery rates of 10-14%[11,107,119] for CD and 3-6%[11,108,122,123] in UC, while one Eastern European cohort observed surgery rates of 10% for CD and 0.5% for UC[21] within the first year of disease. These numbers dating back to the previous decade are comparable to the surgery rates observed in the present cohort, despite patients in the EpiCom cohort being treated earlier and more aggressively with immunomodulators and biologicals in both geographic regions. Thiopurines, accounting for the vast majority of immunomodulators used in this cohort, and biological agents, have both been shown to positively influence the disease course in IBD patients[124,125] and two recent population-based cohorts observed a significant decrease in surgery rates in CD over time in their catchment area associated with an earlier and increased use of thiopurines[110,118].

This finding could not be confirmed in the present cohort although patients received immunomodulators very early in their disease course, possibly because of too short a follow-up. However, a recent randomized controlled trial of severe CD patients also found no benefit to early azathioprine treatment in terms of remission rates and risk of surgery[126]. Surgery rates within three months of diagnosis in the EpiCom cohort were close to the rates at follow-up[73], while stricturing and penetrating behaviour in CD, as well as severe extent in UC, were the main risk factors for surgery, thus suggesting that a proportion of IBD patients present with a disease phenotype that will ultimately require surgery and that this is unavoidable with current treatment strategies.

Disease activity did improve during follow-up and the majority of CD and UC patients were in clinical remission very soon after diagnosis. SCCAI has been shown to correlate well with endoscopy assessment[127,128] while the correlation between HBI scores and mucosal inflammation is poor[129,130]. Since in this study we were not able to follow patients in terms of endoscopic disease activity, the outcomes observed at one year follow-up may not accurately reflect the impact of treatment choices on the course of disease. Long-term follow-up of the EpiCom cohort is necessary in order to accurately determine whether the disease course – in spite of the differences noted in treatment choices, e.g. biological therapy – is in fact similar in Eastern and Western Europe. The same is true for the question of whether early and aggressive treatment with immunomodulators and biologicals can change the natural history and risk of progression of IBD[107,108,131,132].

Only a very small number of patients were diagnosed with cancer or died during follow-up comparable to previous cohorts [94,109,133] and no differences were noted in this regard between Eastern and Western Europe.

5.7 IMPROVEMENTS IN HEALTH-RELATED QUALITY OF LIFE DURING THE FIRST YEAR AFTER DIAGNOSIS

No regional differences were observed in CD and UC patients' disease-specific or generic HRQoL at diagnosis – with the exception of Western European UC patients – or at follow-up. No previous inception cohort study has assessed disease-specific or generic HRQoL within the first year subsequent to diagnosis; however previous population-based cohorts have shown that IBD patients have a lower perception of generic HRQoL compared to a healthy background population, even several years after diagnosis[134–138]. As such, although all CD and UC patients in this cohort saw a significantly improved generic HRQoL, only Eastern European UC patients achieved SF-12 summary scores comparable to the background population at 12 months follow-up. In terms of disease-specific HRQoL, CD and UC patients both saw an improved HRQoL and a majority of patients in this cohort – who were treated with aggressive immunomodulation and biological therapy disease – achieved SIBDQ scores >50 during follow-up. This is in accordance with previous studies, although these assessed disease-specific HRQoL at a much later point in time of the disease course[137,139,140].

Disease activity and severity have in several studies been described as the strongest predictors of HRQoL[134,136,141–144]. Furthermore, mucosal healing has been associated with achieving a high HRQoL score[145]. In this cohort we were not able to analyze the association of disease activity scores with HRQoL and improvements in disease-specific HRQoL were not associated with a severe disease course. However, in this cohort disease activity improved clinically in the majority of patients, suggesting that adequate medical and/or surgical treatment in these patients induced remission and improved patients' HRQoL.

Besides disease activity, HRQoL in IBD patients is influenced by the QoC received[55,146], especially the amount of disease-specific information[146–148] and education received[149,150]. In the present cohort no regional differences were found regarding patients' reported satisfaction with the amount of information received, which overall was reported to be good, possibly contributing to the improvements in HRQoL observed during the follow-up period. Sources of information were found to be similar, although more Eastern European patients found IBD information on the internet. This is despite major differences in the organization of health care between and within Eastern and Western Europe[25,55] including the differences observed in medical treatment. Interestingly, more Eastern European patients reported having received IBD education despite a more widespread use of, for instance, IBD specialist nurses in Western Europe, who have been shown to improve QoC[151,152], without resulting in any difference in satisfaction with the information received.

5.8 RESOURCE UTILIZATION DURING THE INITIAL YEAR OF DISEASE

Finally, we found high health care costs in both Eastern and Western Europe, with total expenses for diagnostics and medical and surgical treatment in the cohort during the first year following diagnosis exceeding four million Euros. Previous studies have

demonstrated the high economic burden of IBD[153–158] but estimates of resources are varying and difficult to compare due to the large variation in direct and indirect costs and differences in the health care policies between countries, as well as differences in methodology[159] between studies. It is also the case that most previous studies date back to the pre-biological era and thus are somewhat outdated.

In the present inception cohort, costs were mainly incurred by the large number of diagnostic procedures and surgeries, which accounted for two thirds of the total expenditure. This finding is in accordance with the EC-IBD study, where investigations and treatments including surgery required to bring patients into remission resulted in the mean annual cost per IBD patient being highest in the first year of disease while significantly decreasing thereafter[158]. Long-term follow-up of the EpiCom cohort will tell whether this is still the case or if costs remain high given the introduction of expensive biological therapy in IBD treatment, which even at this early stage accounted for 20% of total expenditures. More recent studies have shown that biological therapy increases total costs of CD patients[160,161] and now accounts for the largest part of IBD patients' health care costs[162]. Prior to the introduction of biological therapy, surgery was found to be the most expensive, but also the most relapse-preventing, means with which to treat CD patients[156]. Long-term follow-up will be able to answer if this is still the case or whether immunomodulators combined with biologicals have a similar effect on disease as well as on costs.

The difference observed in diagnostic strategy – the more frequent use of colonoscopy, bowel x-ray and upper endoscopy – resulted in significantly higher mean costs per UC patient for diagnostics in Eastern Europe. The more frequent use of "unnecessary" diagnostic procedures in addition to colonoscopy in Eastern European UC patients also contributed to this expenditure. Furthermore, a higher cost in surgery for CD was observed in Eastern Europe and this was caused by a higher number of anal surgeries (Study VI) (included in the surgery-category for the cost analysis) in Western European CD patients. As we observed no differences in disease classification between Eastern and Western Europe, the cost disparities could be caused by differences in medical decision-making or by economic considerations and differences regarding reimbursement rules and national economic guidelines, e.g. starting with a sigmoidoscopy followed by colonoscopy if findings were positive for IBD. In this study we did not use local prices but unified expenses using the Danish DRG price index for all countries without matching prices in individual countries with gross national product. Thus we are able to present the influence of excessive diagnostics and look at the specific costs of frequent biological use, but cannot say definitively what causes these differences.

5.9 STRENGTHS AND LIMITATIONS

The primary strength of the present thesis is that the EpiCom cohort is a prospective, population-based inception cohort of unselected IBD patients diagnosed within well-defined geographical areas. Diagnostic criteria, case ascertainment methods, as well as intervals of follow-up visits and recorded data, were standardised by definition and restricted accordingly, thereby making patients comparable. Several measures described above helped to ensure that all centres performed a population-based cohort study and collected accurate and valid clinical data. Furthermore, regarding the environmental factor questionnaire, the diagnostic delay and the fact that patients answered the questionnaire very soon after the diagnosis helped reduce the risk of recall bias concerning, e.g. dietary habits, prior to the IBD diagnosis. HRQoL and QoC were assessed at relevant time points in the disease course in order to investigate the initial year of disease.

However several limitations, besides those already mentioned, need to be taken into consideration. First, the investigation of IBD management in Europe is influenced by the heterogeneity of the health care systems – such as the reimbursement rules for treatment and procedures, insurance systems, and budgetary restrictions – as choices regarding medical and surgical treatment are strongly linked to extra-medical considerations. However, in terms of patient characteristics, diagnostic procedures and diagnostic delay overall, the regions were similar. Furthermore, the patients' and physicians' perception of QoC and HRQoL may vary within and between the geographical regions and thereby influence the results. This has been shown to affect patients' perception of HRQoL[163–165].

Second, differences in local regulations and requirements for patient consent prohibited a complete follow-up of the EpiCom cohort. Some centres needed consent in order to include any clinical data at all in the database while other centres, e.g. centres from Denmark, only required consent regarding completion of questionnaires. We therefore had to exclude two centres from follow-up as well as 10% of patients from the follow-up cohort.

Third, we were not able to collect data regarding HRQoL, QoC and environmental factors questionnaires on all patients. A group of patients did not answer any questionnaires or only answered some of them, either because they did not give consent or refused to answer some of the questionnaires, while others did not answer them at the required point in time which might have influenced the comparability of the data. However, in terms of socio-demographic characteristics these patients did not differ significantly from those who answered the questionnaires.

Fourth, the method of administering the questionnaires differed between patients. Depending on the patients' educational level, whether local translations of the questionnaires were available, and according to local logistical factors, the questionnaires were either interview-administered by the physician or self-administered by the patients. This could have biased results since patients might not have given sincere answers when face-to-face with a doctor. However for IBDQ, at least, this has been shown not to affect scores significantly[166]. Fifth, the environmental factors and QoC questionnaire were not validated and have not been properly forward/backward translated into languages other than English. To our knowledge, no other environment factor questionnaire was available at the time the protocol was written. A questionnaire on QoC was available from the former EC-IBD group[167], however, it was decided by the EpiCom study group to create a new questionnaire that better fitted the needs of this study.

6. CONCLUSION

This thesis has described the incidence of IBD, as well as several aspects of the course of disease during the first year subsequent to diagnosis across Eastern and Western Europe. We have shown that it is possible to perform a large, entirely web-based epidemiological population-based cohort study throughout Europe using a database enabling participation regardless of prior experience with population-based cohort studies and cost constraints.

We found that the occurrence of CD and UC is twice as high in Western European centres as in Eastern European centres when the inclusion period, case ascertainment methods and diagnostic criteria are standardised across all centres. The highest incidence in the world of IBD combined is found on the Faroe Islands. The

two-to-one incidence gradient observed between Western and Eastern European countries could not be explained by marked differences in environmental factors prior to IBD diagnosis, as Eastern European patients had higher frequencies of dietary risk factors (dietary fibre, sugar intake, and fast food consumption) than Western European patients, while factors such as smoking and oral contraceptives occurred just as frequently.

Eastern and Western European IBD patients were comparable in terms of socio-economic characteristics as well as clinical presentation at diagnosis. Furthermore, the availability of diagnostic tools and the diagnostic strategies did not differ significantly, and in fact were often better in Eastern Europe in terms of the use of colonoscopies and diagnostic delay. Health care systems in Europe are heterogeneous and we found that biological therapy was used more often in Western European patients, while 5-ASA was more widely used for UC and CD patients in Eastern Europe. We also noted that patients in this cohort were treated earlier and more frequently with immunomodulators as compared to previous cohorts. However, this was not found to have an impact on disease course at this early stage as surgery and hospitalization rates during the first year after diagnosis were comparable between Eastern and Western Europe, as well as between the present cohort and previous cohorts. Nonetheless, by the end of the first year subsequent to diagnosis we found that the majority of IBD patients were indolent regarding disease activity.

Patients in Eastern and Western Europe did not differ in their perception of HRQoL within the study period and in both regions patients experienced an improved HRQoL between diagnosis and follow-up. Differences in how, and from whom, patients received disease-specific education and information were noted between the geographical regions; for instance IBD specialist nurses were not used in Eastern European IBD centres. Expenses for the cohort during the initial year of disease exceeded four million Euros, with most money spent on diagnostics and surgery. Biological therapy accounted for one fourth of costs in Western European CD patients.

7. PERSPECTIVES

Long-term follow-up after five and ten years of the EpiCom cohort is needed in order to assess whether the earlier and more frequent treatment with immunomodulators and biologicals observed in this study will change the natural disease course and phenotypes over time or merely postpone outcomes such as surgery. Furthermore, if and how differences in treatment choices between Eastern and Western Europe impact on the disease course requires long-term follow-up. Of particular interest is whether the increased use of immunomodulators will result in higher rates of lymphomas[168]. Additionally, long-term follow-up is needed to determine whether environmental factors and regional differences influence disease course. The EpiCom cohort is currently being followed-up until 2015, by which time data across five years will be available.

The EpiCom study group has created this inception cohort, as well as the related database, as a framework for further epidemiological studies. Within this well-established network of European epidemiologists it is our goal to heighten the standard of epidemiological research in Europe. Furthermore, the web-based concept of database research will enable cooperation with other scientific groups. A new 2011 inception cohort is currently in progress in order to confirm the observed incidence rates, and future cohorts are planned.

8. SUMMARY

Inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune mediated diseases of unknown aetiology. Traditionally, the highest occurrence of both UC and CD is found in North America and Europe, including Scandinavia and the United Kingdom, while the diseases remain rare in Eastern Europe. Until recently, few population-based cohort data were available on the epidemiology of IBD in Eastern Europe. However, recent studies from Hungary and Croatia have reported steep increases in IBD incidence that means they are now comparable with Western European countries. The reasons for these changes remain unknown but could include an increasing awareness of the diseases, better access to diagnostic procedures, methodological bias in previous studies from Eastern Europe, or real differences in environmental factors, lifestyle and genetic susceptibility.

The aim of this thesis was to create a prospective European population-based inception cohort of incident IBD patients in order to investigate whether an East-West gradient in the incidence of IBD exists in Europe. Furthermore, we investigated possible differences throughout Europe during the first year subsequent to diagnosis in terms of clinical presentation, disease outcome, treatment choices, frequency of environmental risk factors, as well as patient-reported health-related quality of life (HRQoL) and quality of care (QoC). Finally, we assessed resource utilization during the initial year of disease in both geographic regions.

A total number of 31 centres from 14 Western and 8 Eastern European countries covering a total background population of approximately 10.1 million participated in this study. During the inclusion period from 1 January to 31 December 2010 a total number of 1,515 patients aged 15 years or older were included in the cohort. Annual incidence rates were twice as high in Western Europe (CD: 6.3/100,000; UC: 9.8/100,000) compared to Eastern Europe (CD: 3.3/100,000; UC: 4.6/100,000), thus confirming a gradient in IBD incidence. The incidence gradient could not be explained by marked differences in environmental factors prior to IBD diagnosis. In fact, Eastern European patients had higher frequencies of dietary risk factors than Western European patients, while the remaining risk factors occurred just as frequently. Furthermore, the availability of diagnostic tools and the diagnostic strategy did not differ, and in fact was better in Eastern Europe in terms of the use of colonoscopies and diagnostic delay.

In terms of socio-economic characteristics as well as clinical presentation at diagnosis Eastern and Western European IBD patients did not differ significantly. However, regarding treatment choices during the initial year of disease the use of biological therapy was significantly higher in Western Europe for both CD and UC, while Eastern European centres used 5-ASA more often in CD and UC. In both regions patients were treated earlier and more frequently with immunomodulators compared to previous cohorts. But despite these differences in treatment, disease course – including hospitalisation and surgery rates during the first year of disease – were similar in both regions and the majority of patients were in clinical remission at follow-up. Finally, generic and disease-specific HRQoL improved in all IBD patients and at twelve months follow-up the majority of patients had a good disease-specific HRQoL score.

Differences in how, and from whom, patients received disease-specific education and information were noted between the geographic regions; for instance IBD specialist nurses were not used in Eastern European IBD centres. Expenses for the cohort during the initial year of disease exceeded four million Euros with

most money spent on diagnostics and surgery. Biological therapy accounted for one fourth costs in Western European CD patients.

Long-term follow-up of the EpiCom cohort is needed in order to assess whether the earlier and more frequent treatment with immunomodulators and biologicals observed in this study will change the natural disease course and phenotypes over time or merely postpone outcomes such as surgery. Furthermore, the question of if and how differences in treatment choices between Eastern and Western Europe impact on the disease course requires long-term follow-up.

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10. APPENDIX

A1. LIST OF PARTICIPANTS

Country	Centre	Background population	Participants			
Western Europe						
Cyprus	Nicosia	240,190	John Kaimakliotis Michael Tryphonos			
Denmark	Aarhus	259,739	Jens F. Dahlerup Lisbet Gerdes Catriona Markussen			
Denmark	Amager	133,939	Soeren Avnstroem Ida Vind			
Denmark	Funen	Adult: 400,575 Pediatric: 84,394	Natalia Pedersen Jens Kjeldsen			
Denmark	Herlev	Adult: 214,431 Pediatric: 49,515	Johan Burisch Pia Munkholm	Dorte Marker Ebbe Langholz		
Denmark	Herning	231,060	Niels Thorsgaard Else Kjær Mikkelsen			
Denmark	Viborg	150,370	Vibeke Andersen Susanne Krabbe			
Faroe Islands	Torshavn (nationwide)	Adult: 38,053 Pediatric: 10,627	Kári R. Nielsen Jóngerð Olsen			
Finland	Pirkanmaa	408,235	Pekka Collin Pia Manninen Birgitta Järventaus			
Greece	Ioanninia	Adult: 162,955 Pediatric: 24,106	Epameinondas V. Tsianos Konstantinos H. Katsanos	Vasileios E. Tsianos Konstantina Stroggili		
Greenland	Nuuk	37,466	Karin Ladefoged			
Iceland	Reykjavík (nationwide)	251,136	Einar Björnsson Gudmundur Ragnarsson			
Ireland	Adelaide and Meath	272,892	Yvonne Bailey Colm O'Morain			
Israel	Beer Sheva	385,222	Selwyn Odes Doron Schwartz			
Italy	Northern Italy*	Adult: 1,674,798 Pediatric: 262,049	Matteo Martinato Vito Annese Marina Beltrami Paolo Bodini Maria Chiara Boni Roberta Caccaro	Angelo De Padova Renata D'Incà Giovanni Fornaciari Iris Frankovic Martina Giannotta Giulia Girardin	Silvia Lombardini Guido Lupinacci Barbara Marani Monica Milla Patrizia Politi Alessia Santini	Susanna Schianchi Giacomo Carlo Sturniolo Silvia Tomasini Daniela Valpiani
Portugal	Vale de Sousa	278,722	Fernando Magro Luisa Manuela Barros			
Spain	Vigo	Adult: 498,880 Pediatric: 74,172	Vicent Hernandez Alberto Villaverde David Martinez-Ares	Luciano Sanromán Carlos Salgado Juan R. Pineda	Luisa de Castro Santos Pereira Jesus Martinez-Cadilla	Ignacio Garcia-Burriel Amalia Carmona Carlos Gonzalez-Portela
Sweden	Linköping	143,473	Sven Almer Lotta Granberg Benoît Almer			
Sweden	Örebro	147,395	Jonas Halfvarson Yaroslava Zhulina	Ulla-Britt Widén Curt Tysk		
United Kingdom	Brent and Harrow	382,616	Naila Arebi Ailsa Hart Sherill Tripoli			
United Kingdom	Hull and East Yorkshire	502,900	Shaji Sebastian			
Eastern Europe						
Croatia	Zagreb	190,558	Boris Vucelic Silvija Cukovic-Cavka	Marko Brinar Niksa Turk		
Czech Republic	Prague	Adult: 180,858 Pediatric: 37,322	Dana Duricova Milan Lukas Martin Bortlik			
Czech Republic	South Bohemia	545,786	Olga Shonová			
Estonia	Southern Estonia	Adult: 291,091 Pediatric: 53,699	Riina Salupere			
Hungary	Veszprem province	Adult: 252,461 Pediatric: 42,564	Peter Laszlo Lakatos Laszlo Lakatos	Zsuzsanna Vegh Szabina Kramli		
Lithuania	Kaunas	Adult: 374,595 Pediatric: 64,225	Limas Kupcinskas Gediminas Kiudelis	Ruta Kucinskiene Laimas Jonaitis		
Moldova	Chisinau	232,597	Svetlana Turcan			
Moldova	Chisinau, pediatric centre	595,496	Ion Mihu Olga Tighineanu Viorica Pleşca			
Romania	Timis	581,850	Adrian Goldis Daniela Lazar			
Russia	Moscow	510,083	Elena Belousova Inna Nikulina			

*The Italian centre consisted of five regions: Padua, Florence, Cremona & Crema, Forlì and Reggio Emilia.

A2. PATIENT CHARACTERISTICS OF 1,367 INCIDENT PATIENTS WITH INFLAMMATORY BOWEL DISEASE INCLUDED IN THE FOLLOW-UP COHORT

	Western European centres			Eastern European centres		
	CD	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
No. of patients (%)	405 (37%)	562 (51%)	142 (13%)	104 (40%)	148 (57%)	6 (2%)
Male (%)	209 (52%)	325 (58%)	70 (49%)	61 (59%)	84 (57%)	4 (67%)
Age at diagnosis, years	35 (16-89)	40 (15-89)	38 (16-84)	32 (15-78)	37 (15-81)	30 (20-34)
Median time to diagnosis, months	4.6 (0-31 yr.)	2.5 (0-21 yr.)	2.3 (0-30 yr.)	3.4 (0-10 yr.)	2.3 (0-20 yr.)	2.7 (0-3 yr.)
Never smoked	165 (43%)	279 (56%)	65 (52%)	38 (37%)	79 (54%)	4 (67%)
Current smoker	137 (35%)	47 (9%)	19 (15%)	39 (38%)	16 (11%)	2 (33%)
Former smoker	85 (22%)	174 (35%)	41 (33%)	25 (25%)	52 (35%)	0 (0%)
Disease extent						
E1: Proctitis		118 (21%)			32 (22%)	
E2: Left-sided		225 (41%)			67 (45%)	
E3: Extensive colitis		210 (38%)			49 (33%)	
Disease location						
L1: Terminal ileum	118 (30%)			40 (39%)		
L2: Colon	112 (28%)			20 (20%)		
L3: Terminal ileum + colon	87 (22%)			25 (25%)		
L4: Upper GI	30 (8%)			2 (2%)		
L1+L4	23 (6%)			5 (5%)		
L2+L4	11 (3%)			3 (3%)		
L3+L4	18 (5%)			7 (7%)		
Disease behaviour						
B1: non-stricturing, non-penetrating	259 (64%)			70 (67%)		
B2: stricturing	79 (20%)			20 (19%)		
B3: penetrating	29 (7%)			6 (6%)		
B1p: B1 + perianal	16 (4%)			1 (1%)		
B2p: B2 + perianal	3 (1%)			0 (0%)		
B3p: B3 + perianal	19 (5%)			7 (7%)		

A3. PATIENT CHARACTERISTICS OF 1,079 INCIDENT PATIENTS WITH INFLAMMATORY BOWEL DISEASE INCLUDED IN THE QUALITY OF LIFE COHORT

	Western European centres			Eastern European centres		
	CD	UC	IBDU	CD	UC	IBDU
No. of patients (%)	305 (36%)	437 (52%)	96 (11%)	97 (40%)	138 (57%)	6 (2%)
Male (%)	160 (52%)	240 (55%)	47 (49%)	56 (58%)	77 (56%)	4 (67%)
Age at diagnosis, years	35 (16-89)	39 (15-89)	39 (17-77)	31 (15-78)	36 (18-81)	30 (20-34)
Time to diagnosis, months	4.6 (0-374)	2.4 (0-255)	2.4 (0-362)	3.4 (0-125)	2.2 (0-240)	2.7 (0-38)
Smoking status at diagnosis						
Never smoked	122 (41%)	233 (55%)	45 (49%)	35 (36%)	76 (55%)	4 (67%)
Current smoker	107 (36%)	35 (8%)	14 (15%)	36 (38%)	14 (10%)	2 (33%)
Former smoker	71 (24%)	155 (37%)	33 (36%)	25 (26%)	48 (35%)	0 (0%)
Educational status						
Academic education	65 (22%)*	81 (20%)*	16 (18%)	14 (15%)	38 (28%)	0 (0%)
Non-academic education	159 (53%)*	235 (57%)*	48 (53%)	51 (53%)	66 (48%)	6 (100%)
Currently attending education	46 (15%)*	48 (12%)*	7 (8%)	26 (27%)	27 (20%)	0 (0%)
No education	28 (9%)*	46 (11%)*	20 (22%)	5 (5%)	7 (5%)	0 (0%)
Employment status						
Employed	155 (52%)	225 (54%)	51 (55%)	47 (49%)	76 (55%)	5 (83%)
Self-employed	17 (6%)	29 (7%)	6 (6%)	6 (6%)	5 (4%)	0 (0%)
Unemployed	45 (15%)	42 (10%)	11 (12%)	14 (15%)	9 (7%)	1 (17%)
Student	47 (16%)	54 (13%)	10 (11%)	20 (21%)	22 (16%)	0 (0%)
Retired	35 (12%)	68 (16%)	15 (16%)	9 (9%)	26 (19%)	0 (0%)
Extra-intestinal manifestations at diagnosis						
None	266 (86%)	391 (89%)	82 (84%)	82 (82%)	120 (86%)	5 (83%)
Skin	6 (2%)	8 (2%)	4 (4%)	2 (2%)	1 (1%)	0 (0%)
Eyes	4 (1%)	6 (1%)	3 (3%)	2 (2%)	1 (1%)	0 (0%)
Joints	28 (9%)	31 (7%)	7 (7%)	12 (12%)	13 (9%)	1 (17%)
Primary Sclerosing Cholangitis (PSC)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Pancreatitis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Other	4 (1%)	4 (1%)	2 (2%)	2 (2%)	1 (1%)	0 (0%)
Disease extent at diagnosis						
E1: Proctitis	85 (19%)			26 (19%)		
E2: Left-sided	185 (42%)			64 (46%)		
E3: Extensive colitis	167 (38%)			48 (35%)		
Disease location at diagnosis						
L1: Terminal ileum	87 (29%)			37 (39%)		
L2: Colon	83 (28%)			19 (20%)		
L3: Terminal ileum + colon	70 (23%)			23 (24%)		
L4: Upper GI	22 (7%)			2 (2%)		
L1+L4	19 (6%)			5 (5%)		
L2+L4	7 (2%)			3 (3%)		
L3+L4	13 (4%)			7 (7%)		
Disease behaviour at diagnosis						
B1: non-stricturing, non-penetrating	184 (60%)			66 (68%)		
B2: stricturing	60 (20%)			18 (19%)		
B3: penetrating	28 (9%)			5 (5%)		
B1p: B1 + perianal	14 (5%)			1 (1%)		
B2p: B2 + perianal	3 (1%)			0 (0%)		
B3p: B3 + perianal	16 (5%)			7 (7%)		

* Difference between geographic regions, p<0.05

A4. PATIENT CHARACTERISTICS OF 1,182 INCIDENT PATIENTS WITH INFLAMMATORY BOWEL DISEASE ANSWERING THE IOIBD ENVIRONMENTAL FACTORS QUESTIONNAIRE

	Western European centres			Eastern European centres		
	CD	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
No. of patients (%)	345 (37%)	483 (52%)	105 (11%)	99 (40%)	144 (58%)	6 (2%)
Male (%)	181 (52%)	269 (56%)	51 (49%)	58 (59%)	82 (57%)	4 (67%)
Age at diagnosis, years	35 (16-89)	39 (15-89)	38 (17-79)	31 (15-78)	36 (18-81)	30 (20-34)
Time to diagnosis, months	4.6 (0-374)	2.5 (0-255)	2.5 (0-362)	3.3 (0-126)	2.2 (0-240)	2.7 (0-38)
First degree relative with IBD	34 (10%)	55 (11%)	18 (17%)	7 (7%)	10 (7%)	1 (17%)
Extra-intestinal complications						
None	299 (87%)	436 (90%)	90 (86%)	83 (84%)	127 (88%)	5 (83%)
Skin	3 (1%)	6 (1%)	2 (2%)	2 (2%)	0 (0%)	0 (0%)
Eyes	4 (1%)	3 (1%)	2 (2%)	0 (0%)	1 (1%)	0 (0%)
Joints	33 (10%)	32 (7%)	8 (8%)	13 (13%)	12 (8%)	1 (17%)
Primary Sclerosing Cholangitis	0 (0%)	2 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Pancreatitis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Other	4 (1%)	4 (1%)	3 (3%)	2 (2%)	1 (1%)	0 (0%)
Disease extent at diagnosis						
E1: Proctitis	95 (20%)			29 (20%)		
E2: Left-sided	204 (42%)			67 (47%)		
E3: Extensive colitis	184 (38%)			48 (33%)		
Disease location at diagnosis						
L1: Terminal ileum	101 (30%)			38 (39%)		
L2: Colon	88 (26%)			20 (20%)		
L3: Terminal ileum + colon	79 (23%)			24 (24%)		
L4: Upper GI	25 (7%)			1 (1%)		
L1+L4	22 (6%)			5 (5%)		
L2+L4	10 (3%)			3 (3%)		
L3+L4	16 (5%)			7 (7%)		
Disease behaviour at diagnosis						
B1: non-stricturing, non-penetrating	212 (61%)			67 (68%)		
B2: stricturing	70 (20%)			19 (19%)		
B3: penetrating	28 (8%)			5 (5%)		
B1p: B1 + perianal	15 (4%)			1 (1%)		
B2p: B2 + perianal	3 (1%)			0 (0%)		
B3p: B3 + perianal	17 (5%)			7 (7%)		

* Difference between geographic regions, p<0.05

A5. PATIENT CHARACTERISTICS OF 947 INCIDENT PATIENTS WITH INFLAMMATORY BOWEL DISEASE ANSWERING THE QUALITY OF CARE QUESTIONNAIRE

	Western European centres			Eastern European centres		
	CD	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
No. of patients (%)	276 (38%)	361 (50%)	93 (12%)	87 (40%)	124 (57%)	6 (3%)
Male (%)	145 (53%)	207 (57%)	44 (47%)	50 (58%)	69 (56%)	4 (67%)
Age at diagnosis, years	37 (16-89)	40 (15-89)	39 (17-77)	31 (15-78)	35 (18-80)	30 (20-34)
Time to diagnosis, months	4.0 (0-31 yr.)	2.3 (0-21 yr.)	2.3 (0-30 yr.)	3.4 (0-10 yr.)	2.3 (0-20 yr.)	2.7 (0-3 yr.)
Smoking status at diagnosis						
Never smoked	111 (41%)	183 (53%)	44 (51%)	30 (35%)	67 (54%)	4 (67%)
Current smoker	95 (35%)	27 (8%)	10 (11%)	32 (37%)	12 (10%)	2 (33%)
Former smoker	66 (24%)	135 (39%)	33 (38%)	24 (28%)	45 (36%)	0 (0%)
Educational status						
Academic education	63 (23%)*	70 (21%)*	16 (19%)	14 (16%)	36 (29%)	0 (0%)
Non-academic education	149 (55%)*	191 (57%)*	45 (53%)	48 (56%)	57 (46%)	6 (100%)
Currently attending education	35 (13%)*	39 (12%)*	7 (8%)	20 (23%)	25 (20%)	0 (0%)
No education	23 (9%)*	35 (10%)*	17 (20%)	4 (5%)	6 (5%)	0 (0%)
Employment status						
Employed	142 (52%)	183 (54%)	48 (55%)	43 (50%)	70 (56%)	5 (83%)
Self-employed	15 (6%)	25 (7%)	6 (7%)	4 (5%)	5 (4%)	0 (0%)
Unemployed	42 (15%)	30 (9%)	10 (12%)	14 (16%)	5 (4%)	1 (17%)
Student	40 (15%)	45 (13%)	10 (12%)	17 (20%)	22 (18%)	0 (0%)
Retired	33 (12%)	59 (17%)	12 (14%)	8 (9%)	22 (18%)	0 (0%)
Disease extent at diagnosis						
E1: Proctitis	67 (19%)			24 (19%)		
E2: Left-sided	149 (41%)			56 (45%)		
E3: Extensive colitis	145 (40%)			44 (36%)		
Disease location at diagnosis						
L1: Terminal ileum	72 (26%)			32 (37%)		
L2: Colon	79 (29%)			18 (21%)		
L3: Terminal ileum + colon	62 (23%)			21 (24%)		
L4: Upper GI	23 (8%)			1 (1%)		
L1+L4	18 (7%)			5 (6%)		
L2+L4	7 (3%)			3 (3%)		
L3+L4	11 (4%)			6 (7%)		
Disease behaviour at diagnosis						
B1: non-stricturing, non-penetrating	162 (59%)			57 (66%)		
B2: stricturing	60 (22%)			17 (20%)		
B3: penetrating	24 (9%)			5 (6%)		
B1p: B1 + perianal	12 (4%)			1 (1%)		
B2p: B2 + perianal	3 (1%)			0 (0%)		
B3p: B3 + perianal	15 (5%)			7 (8%)		

* Difference between geographic regions, p<0.05