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Cohort Profile

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Cohort Profile: The Inflammatory Bowel Disease South Limburg Cohort (IBDSL)

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Why was the cohort set up?

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the intestines, which may have severe impact on patients' quality of life.[1–3] IBD is characterized by sequences of exacerbation and remission, and is considered to arise from complex interactions between an altered intestinal immune response, the intestinal microbiota and environmental factors in a genetically susceptible host.[4] Its presentation is heterogeneous, and also treatment response varies. In the IBD field, identification and validation of biomarkers to predict disease course and therapy response is currently an important challenge. Also, the further unravelling of (biological) disease mechanisms remains of paramount importance, especially with regard to the development of exacerbations.

The Inflammatory Bowel Disease South Limburg (IBDSL) cohort is a long-term, ongoing, population-based cohort with deep phenotyping and clinical data, and an extensive biomaterial collection (referred to as the IBDSL biobank). The IBDSL cohort started in 1991 as part of the European Collaborative study on Inflammatory Bowel Disease (EC-IBD).[5] Twenty centres throughout Europe began registering all newly diagnosed patients in order to study a hypothesized North-South gradient in IBD incidence. IBDSL proceeded with registering patients and their clinical data, and has been studying IBD epidemiology, disease course, risk factors for disease onset and development, and quality of life, ever since. As of 2011, the cohort is being scaled up into a population-based biobank and the focus expanded towards exploring underlying biological disease mechanisms and molecular epidemiology. Population-based biomaterial collections, representing the full heterogeneous IBD spectrum (from mild to severely diseased), are well equipped for this research and warranted.

IBDSL is a Dutch consortium comprising the gastroenterology departments of Maastricht University Medical Centre+ (MUMC+) and the general district hospitals Orbis MC Sittard-Geleen and Atrium MC Heerlen. IBDSL has been approved by the Ethics Committee of the Maastricht University Medical Centre+ (NL31636.068.10), meets the ethical standards of the revised version of the Declaration of Helsinki and is registered at www.ClinicalTrial.gov (NCT02130349).

Who is in the cohort?

Design

The IBDSL cohort is a long-term, population-based, prospective, inception IBD cohort with a cross-sectional biobank.

Setting

South Limburg is a geographical area in the southeast of The Netherlands, bordered by Belgium and Germany (Figure 1). In January 2014, South Limburg had 604 154 inhabitants.[6] Apart from the general district hospitals of Heerlen and Sittard-Geleen, the Maastricht University Medical Centre+ and general practitioners, no other in- or outpatients clinics are entrusted with IBD care in this area. As cross-border health care is limited and migration rates are rather low,[6] South Limburg provides an ideal setting for population-based research.

All IBD patients, diagnosed above 18 years of age and living in South Limburg at time of diagnosis, are eligible. IBD is diagnosed by certified gastroenterologists according to the Lennard-Jones criteria[7] and proven by endoscopic, radiological and/or histological findings.

IBDSL cohort study population

To capture the full South Limburg IBD population, we use a multifaceted approach. First, newly diagnosed patients are registered prospectively by the gastroenterologists and IBD nurses of the participating hospitals. Second, any missed patients are identified through regular hospital administration checks. Finally, we cooperate with PALGA, a histopathology registry covering all pathology reports generated in The Netherlands (since 1991),[8] to identify IBD patients who do not attend hospitals.

In Table 1 an overview is shown of the IBDSL cohort study population (with minimum follow-up of 2 years). In January 2014, this comprised 2837 IBD patients, of whom 1162 were diagnosed with CD and 1675 with UC. The study population represents over 93% of all eligible patients in South Limburg, determined by comparing IBDSL cases with IBD cases of a representative sample of 18 South Limburg general practitioners (GP). In The Netherlands, GPs are the first to be contacted for health care. Therefore, IBD patients in referral care are also known in GP registries, which make them suitable for assessing completeness.

The remaining 7% could not be captured for ethical and logistic reasons. Hence, we were not able to compare IBD phenotypes between included and missed patients (i.e. comparison according to the Montreal classification[9] which considers age of onset, disease location/extent and behaviour). Selection bias, however, is not expected; phenotypes that can easily be missed in non-population-based cohorts, such as mildly diseased patients not attending hospitals, are captured via PALGA. The remaining 7% of patients mostly likely have an IBD diagnosis without endoscopic, radiological and/or histological confirmation (and do not meet IBDSL inclusion criteria), may be misdiagnosed (e.g. irritable bowel syndrome rather than IBD) or attend Belgian or German hospitals. As guidelines in these countries are similar to those in The Netherlands, as well as costs (cross-border health care is also covered by insurers), it is highly unlikely that cross-border health care is associated with a specific IBD phenotype.

Figure 1. Geographic location of South Limburg, including the IBDSL consortium centers: Maastricht University Medical Center+ (MUMC+), Atrium Medical Center Heerlen (Atrium MC) and Orbis Medical Center Sittard-Geleen (Orbis MC).

IBDSL biobank study population

All patients in the IBDSL cohort are also eligible for biomaterial donation. An overview of the biobank study population is shown in Table 2. In January 2014, 957 IBD patients were biobanked, of whom 535 had CD and 422 had UC. At this moment the biobank is still in progress of becoming population based. Donation response rates are high among all phenotypes, and based thereupon we expect to biobank approximately 75% of all patients in the cohort.

How often have they been followed up?

IBDSL cohort

Patient registration began in January 1991, and has been embedded in daily clinical practice. Gastroenterologists and IBD nurses completed a standardized registration form for any newly diagnosed patient, and clinical and

Table 1. Baseline characteristics of the IBDSL cohort study population with minimum 2-year follow-up in January 2014, and characteristics of loss to follow-up

Baseline		UC	CD
Patients	N	1675	1162
Age at diagnosis	mean in yrs (SD)	46.2 (16.8)	37.7 (15.9)
Disease duration	mean in yrs (SD)	9.1 (5.9)	8.4 (5.9)
Males	N (%)	895 (53)	434 (37)
Extent at diagnosis[a]			
E1/E2/E3	N (%)	568 (34) / 791 (48) / 299 (18)	–
Location at diagnosis[a]			
L1/L2/L3/L4	N (%)	–	500 (43) / 371 (32) / 267 (23) / 24 (2)
Behaviour at diagnosis[a]			
B1/B2/B3	N (%)	–	900 (77) / 177 (15) / 85 (7)
Follow-up		**UC**	**CD**
Death	N	202	77
Males	N (%)	130 (64)[b]	29 (38)
E1/E2/E3[a]	N (%)	44 (22) / 118 (60) / 35 (18)[b]	–
L1/L2/L3/L4[a]	N (%)	–	32 (42) / 33 (43) / 10 (13) / 2 (3)
B1/B2/B3[a]	N (%)	–	64 (83) / 5 (6) / 8 (10)
Migrated	N	101	51
Males	N (%)	58 (57)	23 (45)
E1/E2/E3[a]	N (%)	32 (32) / 47 (47) / 21 (21)	–
L1/L2/L3/L4[a]	N (%)	–	22 (43) / 18 (35) / 10 (20) / 1 (2)
B1/B2/B3[a]	N (%)	–	40 (78) / 7 (14) / 4 (8)

UC, ulcerative colitis; CD, Crohn's disease; N, number of patients; yrs, years; SD, standard deviation.

[a]Phenotype according to Montreal Classification. Disease extent of UC was defined as: ulcerative proctitis (E1, limited to the rectum), left sided UC (E2, limited to a proportion of the colorectum distal to the splenic flexure) and extensive UC (E3, proximal to the splenic flexure). CD location was defined as: ileal involvement (L1), exclusive colonic involvement (L2), ileocolonic involvement (L3) or isolated upper disease (L4). CD behaviour was defined as: non-stricturing and non-penetrating (B1), stricturing (B2) or penetrating (B3).

[b]Significant difference ($P < 0.01$) in a chi-square analysis of deceased vs living patients ($\alpha = 0.05$).

demographic data at time of diagnosis were assessed. For patients captured through hospital administration or PALGA, data (at time of diagnoses) were assessed retrospectively, immediately after case identification. Clinical and demographic data were updated biennially until loss to follow-up (i.e. death or migration outside the region). Patient identification and follow-up is an ongoing process.

In Table 1, characteristics of loss to follow-up are described. Loss to follow-up by either death or migration was evenly distributed among gender and phenotypes in CD. In UC, loss to follow-up by death was more pronounced in male patients and in patients with left-sided colitis at diagnosis. Such higher proportions of males and left-sided inflammation were also found in our elderly-onset UC population (>60 years), when compared with adult-onset (<60 years).[10] A shorter life expectancy of the former may lead to the observed skewness in loss to follow-up by death.

IBDSL biobank

Biomaterial collection began in 2011, using a cross-sectional approach. Biomaterial collection has also been embedded in daily clinical practice; after consulting their gastroenterologist or IBD nurse, patients were requested to participate in biomaterial collection. Patients not attending the hospital regularly were either visited at home or invited to the hospital. In addition, a subgroup of IBD patients were invited for repeated sampling, and they donated biomaterial at every hospital visit for 2 years. We have permission to contact biobanked patients for additional biomaterial donation in future.

Table 2. Characteristics of biomaterial collected in the IBDSL biobank, until January 2014

		UC	CD
Biomaterial	N	422	535
DNA	N	390	463
Plasma	N	390	463
Serum	N	414	524
Faeces	N	327	405

UC, ulcerative colitis; CD, Crohn's disease; N, number of patients.

Table 3. Overview of collected data and biomaterial in IBDSL cohort, biobank and subgroups

IBDSL cohort (population-based)	IBDSL biobank (population-based, in progress)
Baseline clinical data	Biomaterial
Date of diagnosis	DNA
IBD phenotype (location/extent/behaviour)	Plasma
IBD extra-intestinal manifestations	Serum
IBD complications	Faeces
IBD medication	
IBD surgery	Data
Pathology reports	CD clinical activity score (HBI)
Endoscopy reports	UC clinical activity score (SCCAI)
Radiology reports	
	Subgroups (subset of IBDSL biobank)
Baseline questionnaire	
Demographics	
Smoking	Endoscopy subgroup
Socioeconomic status	Biomaterial (as in biobank)
	Biopsies
Follow-up data (biennial follow-up)	CD endoscopic activity score (SES-CD)
Clinical data (as baseline)	UC endoscopic activity score (Mayo score)
Questionnaires (e.g. QoL)	
Linkage local authority database	Repeat sampling subgroup
Linkage hospital database[a]	Biomaterial (as in biobank, bimonthly)
Linkage local pharmacies[a]	Exhaled air
	FFQ[a]

QoL, Quality of Life questionnaire; CD, Crohn's disease; UC, ulcerative colitis; HBI, Harvey Bradshaw Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's disease; FFQ, Food Frequency Questionnaire.
[a]Under development.

What has been measured?

An overview of collected data and biomaterials is shown in Table 3.

IBDSL cohort

Baseline data were collected for time of diagnosis, which was set as the date of endoscopic or radiological examination with first evidence for IBD. Case report forms (CRF) were completed and comprised phenotype (Montreal classification, i.e. age of onset, disease location/extent, behaviour), extra-intestinal manifestations (eyes, mouth, skin, liver, joints), IBD complications (stenosis, fistula, abscess, thrombosis, perforation, osteoporosis, osteopenia), IBD medication (type, dosage and duration), IBD surgery (type and date), pathology reports, endoscopy reports and radiology reports. For CD patients, disease location at diagnosis was only set after 1 year, as many patients did not have a complete diagnostic workup at time of diagnosis. In addition, data on demographics, smoking and socioeconomic status were collected from all patients.

Biennially, clinical and demographic data were updated through chart review and questionnaires. Patients' charts were reviewed by a trained nurse, and CRFs similar to those described above were completed. Questionnaires always comprised quality of life [i.e. Short Inflammatory Bowel Disease Questionnaire (S-IBDQ), Short Form 36 health survey (SF-36)], in addition to different topics each time such as medication adherence, subfertility, fatigue and stress. IBDSL is also linked to the Dutch resident registration for updates on addresses and vital status.

IBDSL biobank

Biomaterial was collected using standardized operating procedures, and comprised one serum tube, one plasma tube and one faeces tube. At the same time, clinical disease activity was determined by the Harvey Bradshaw Index for CD[11] and the Simple Clinical Colitis Activity Index for UC.[12]

Serum tubes (8.5 ml, BD, Plymouth, UK) were centrifuged within 4 h after collection (3000 G, 10 min, 4°C, without brake). Plasma tubes (10.0 ml, BD, Plymouth, UK) were also centrifuged within 4 h after collection (1800 G, 10 min, room temperature (RT), with brake). DNA was isolated from the buffy coat using the FlexiGene DNA Kit (Qiagen, Venlo, The Netherlands). After processing, all

aliquots were stored at −80°C in the certified MUMC+ biobank.[13]

IBDSL biobank subgroups

The IBDSL biobank comprises two subgroups, in which additional biomaterial was collected. Consecutive patients who were scheduled for routine endoscopy and consented to donate biopsies, took part in the 'endoscopy subgroup' ($n = 104$). A maximum of six biopsies were collected (two terminal ileum, two ascending colon, two descending colon, preferably inflamed tissue), in addition to an endoscopic disease activity score (Simple Endoscopic Activity Score for CD[14] and Mayo endoscopic subscore for UC[15]) and the previously described set of serum, plasma, faeces and clinical activity scores. Biopsies were collected in a cryogenic vial (1.5 ml, Thermo Scientific Nalgene, Rochester, USA), snap-frozen in liquid nitrogen and stored at −80°C. This subgroup can be used as a reference cohort for validation purposes, since intestinal inflammation was determined by the gold standard (endoscopy).

A second group of patients were invited for repeat sampling. In this 'repeat sampling subgroup' ($n = 323$) patients donated serum, plasma and faeces at every hospital visit for 1 year. These patients also donated exhaled air for volatile organic compounds (VOC) metabolomics. Each patient was asked to inflate a 5-l Tedlar bag (SKC Ltd, Dorset, UK). Captured VOCs were transferred to carbon-filled sorption tubes (Markes International Ltd, Llantrisant Business Park, UK) and trapped within 2 h after collection. As this subgroup comprises patients going from active disease into remission, and vice versa, it enables testing biomarker consistency over time and in different stages of the disease.

Future

Several plans to improve IBDSL are scheduled. First, direct linkage of the IBDSL cohort to the hospital databases is currently under development, which will result in an immediate cohort udate every time a specialist adds information to the medical file. This update also includes laboratory analyses. Second, linkage to local pharmacies has been initiated. Third, patients with an IBD diagnosis during childhood are not captured at this moment, just as IBD-undefined patients (IBD-U, IBD patients in which a clear distinction between UC and CD cannot be made). Current efforts are being made to expand IBDSL in order to include these patients. We also started a new study to expand the repeat sampling subgroup with dietary data such as food frequency questionnaires (FFQ) at baseline. Finally, we have permission to include a control group of patients' partners and family members, who will also be invited to donate biomaterial.

What has it found? Key findings and publications

During its existence, IBDSL has participated in several international consortia. IBDSL was a founding member of the EC-IBD, which studied IBD epidemiology in Europe.[5] Nowadays, IBDSL is involved in three international consortia (Sysmed-IBD,[16] IBD-BIOM[17] and IBD-Character[18]), which are funded by the European Commission's Seventh Framework Programme and focus on the identification and validation of biomarkers. Altogether, 55 scientific papers on IBDSL data have been published so far, either autonomously or as part of the consortia.[1,5,19–71] Below, a short overview is provided of some previous findings, as well as some recent findings which are currently submitted for publication.

IBDSL cohort

Early IBDSL cohort studies focused on epidemiology, risk factors for disease onset and progression, and quality of life. IBDSL, for instance, has provided reliable incidence data on IBD in The Netherlands.[21,23] Between 1991 and 2002, age-standardized incidence rates for CD were 4.84 (per 100 000 person-years) in males and 7.58 in females, and 8.51 and 6.92 for UC, respectively.[21] These incidences were found to be relatively high compared with other European countries,[21,23] and contributed to a North-South gradient in European IBD incidence.[68] We also found age at diagnosis,[20] phenotype at diagnosis[20] and smoking[25] to be predictive for a more severe disease course (the latter only in CD). IBDSL patients often experienced an impaired health-related quality of life as well as fatigue problems (also when in remission)[1] and, despite a normal life expectancy,[19] they encountered difficulties when applying for life insurance.[28]

Recent studies concerned long-term disease outcome and disease course variations between patients diagnosed in different time periods. In both UC and CD, for instance, long-term disease outcome of elderly-onset IBD (>60 years) was similar to adult-onset (<60 years).[10] However, less frequent use of immunomodulating drugs and biologicals [anti-tumour necrosis factor (anti-TNF) drugs] was observed in the former group. Furthermore, early colectomy rate was found to be 2.4-fold lower in UC patients diagnosed after 2006, the year biologicals were first registered for UC in The Netherlands, as compared with patients diagnosed in the era before biological

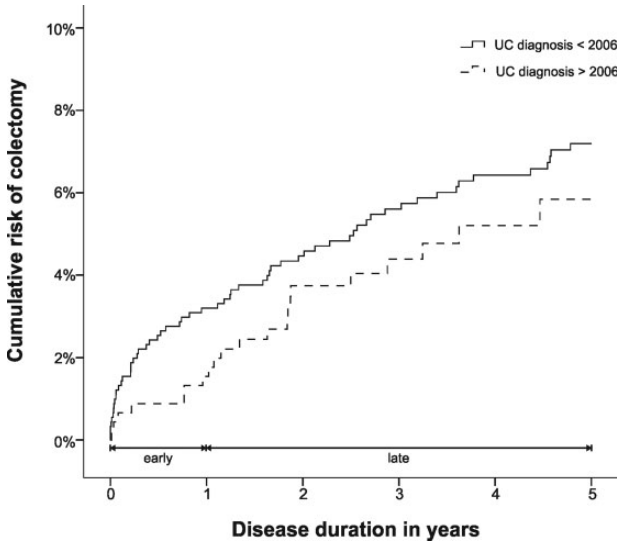

Figure 2. Kaplan-Meier curves of cumulative colectomy risk in UC patients diagnosed before and after 2006. Early colectomy rate was found to be 2.4-fold lower in UC patients diagnosed after 2006, the year biologicals were first registered for UC in the Netherlands, as compared to patients diagnosed in the era before biological availability (<2006). In-depth focus showed these colectomies to be prevented rather than postponed.

availability(<2006).[72] These colectomies seemed to be prevented rather than postponed (Figure 2).

IBDSL biobank

IBDSL biobank studies focused on underlying disease mechanisms and the identification of biomarkers that predict disease course. *Clostridium difficile*[58] and enteropathogenic viruses,[59] for instance, were found not to be common triggers for IBD exacerbations. Microbial composition, on the other hand, changed when remissive IBDSL patients went into subsequent exacerbation, but these changes were rather patient-specific than general.[70] Importantly, use of thiopurine medication also had a significant impact on the microbial composition and diversity, and should be considered when studying the intestinal microbiota in relation to disease course.[70]

In a recent analysis, we investigated whether VOCs in exhaled air can accurately differentiate between active CD and remission.[73] Ileocolonoscopy is currently the gold standard to assess disease activity but, as it is invasive and expensive, alternatives are warranted. In the IBDSL cohort, a set of 10 discriminatory VOCs was found to correctly differentiate between active CD and remission [sensitivity = 0.81, specificity = 0.80, area under the curve = 0.80].[73]

Main strengths and weaknesses?

A major strength lies in the population-based character of the cohort, with a completeness of 93%. Population-based cohorts comprise the full spectrum of IBD phenotypes, from mild to severe disease course, in contrast to referral cohorts which tend to over-represent the latter. This makes IBDSL ideal to study hypotheses that need a population-based design (such as incidence studies, studies on prevalence of disease manifestation, natural disease course and potential modulators thereof), and to confirm findings of other 'referral' cohorts. Although 93% is very high, we acknowledge that not all eligible patients were identified. Selection bias, however, is not expected in view of the factors previously discussed.

In addition to the high level of completeness, the cohort is also characterized by its high stability. South Limburg is bordered by Belgium and Germany, and even though it is allowed, cross-border health care remains limited, as well as migration.[6] South Limburg IBD patients tend to stay within the region and, as only the IBDSL consortium centres (and general practitioners) are entrusted with IBD care, these patients can be followed up quite easily. This provides an ideal setting for population-based research.

Another strength is the long-term and very detailed clinical, demographic and pharmacological data being collected for each patient since diagnosis. As follow-up is done biennially, and as we are connected to the Dutch resident registration (and other databases in future), IBDSL data remains up to date. Also recall bias is minimal, because most data are collected prospectively.

Finally, the extensive collection of biomaterial is a major strength, and makes IBDSL well equipped for investigating underlying molecular, genetic and microbiological mechanisms that initiate or sustain IBD. These biomaterials can also be used for the identification of (non-invasive) markers to predict disease course and therapy response, or to validate such markers if derived from other cohorts. IBDSL is currently building the first population-based IBD biobank. Although it is not population-based yet, it does include a representative sample of our cohort.

Limitations lie in the strict inclusion criteria. The IBDSL cohort does currently not contain any information on IBD patients diagnosed during childhood, nor any IBD-U patients. Plans to include these patients are in progress. Second, due to its invasiveness and the large scale of the cohort, endoscopy could not always be used to determine disease activity at time of biomaterial donation (gold standard). Disease activity was determined by clinical activity scores instead, but these scores are somewhat subjective and, especially for CD, correlation with actual mucosal inflammation is moderate.[74,75] To overcome this, we validated a combination of clinical activity scores and inflammation markers (i.e. C-reactive protein, faecal calprotectin) in the IBDSL endoscopy subgroup, and found

this combi-score to improve distinction of active from inactive disease.[76]

Can I get hold of the data?

We welcome new collaborations to study interesting hypotheses in IBD. Applications for collaboration are first to be approved by the IBDSL committee. Applications should be addressed to Dr Marie Pierik, principal investigator of the IBDSL cohort at IBDSL@maastrichtuniversity.nl.

IBDSL cohort in a nutshell

- The IBDSL cohort is a prospective population-based IBD inception cohort with a cross-sectional biobank, set up to investigate disease course, (molecular) epidemiology and underlying biological mechanisms of IBD.
- Newly diagnosed IBD patients above 18 years of age and living in the Dutch South Limburg region at time of diagnosis were eligible and have been recruited since 1991, whereas biosample collection was implemented in 2011.
- At present 2837 IBD patients (1162 CD / 1675 UC) have been included and followed prospectively (>93% of the total eligible IBD population), of whom 957 patients (535 CD / 422 UC) have been included in the cross-sectional biobank.
- The dataset comprises demographic and clinical data (i.e. phenotype, extra-intestinal manifestations, complications, medication, surgery and pathology, endoscopy and radiology reports) at baseline and follow-up, and the biobank comprises serum, plasma, DNA and faeces (biopsies and exhaled air are collected from a subset).
- We welcome new collaborations, for which requests can be sent to: [IBDSL@maastrichtuniversity.nl].

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Conflict of interest: None declared.

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