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Cohort profile: The Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

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Complete List of Authors:	<p>Salomon, Benita; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Grännö, Olle; Örebro University, Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health Bergemalm, Daniel; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health Strid, Hans ; Karolinska Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology Carstens, Adam; Ersta Hospital, Department of Internal Medicine; Karolinska Institute, Department of Medicine Huddinge Hjortswang, Henrik; Linköping University, Department of Gastroenterology, County Council of Östergötland, Department of Clinical and Experimental Medicine Lundstrom, Maria; Uppsala University, Department of Medical Sciences, Gastroenterology Research Group Hreinsson, Johann; Sahlgrenska Academy, Department of Molecular and Clinical Medicine Almer, Sven; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology; Karolinska Institute, Department of Medicine Solna Bresso, Franscesca; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology; Karolinska Institute, Department of Medicine Solna Eriksson, Carl; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health Grip, Olof ; Skåne University Hospital Lund, Department of Gastroenterology Blomberg, André; Sahlgrenska University Hospital, Department of Medicine, Geriatrics and Emergency Medicine Marsal, Jan; Skåne University Hospital Lund, Department of Gastroenterology Nikaein, Niloofar; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Bakhtyar, Shoaib; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Lindqvist, Carl Mårten; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Hultgren-Hornquist, Elisabeth; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Magnusson, Maria; Sahlgrenska Academy, Department of Microbiology</p>

	and Immunology, Institute of Biomedicine Keita, Åsa; Linköping University, Department of Biomedical and Clinical Sciences D'Amato, Mauro ; LUM Giuseppe Degennaro University, Department of Medicine and Surgery; CIC bioGUNE, Gastrointestinal Genetics Lab; Basque Foundation for Science, Ikerbasque Repsilber, Dirk; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Öhman, Lena; Sahlgrenska Academy, Department of Microbiology and Immunology, Institute of Biomedicine Söderholm, Johan; Linköping University, Department of Biomedical and Clinical Sciences; Linköping University, Department of Surgery Carlson, Marie; Uppsala University, Department of Medical Sciences, Gastroenterology Research Group Hedin, Charlotte; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology; Karolinska Institute, Department of Medicine Solna Kruse, Robert; Örebro University, School of Medical Sciences, Faculty of Medicine and Health; Örebro University, Inflammatory Response and Infection Susceptibility Centre (iRiSC), Faculty of Medicine and Health; Örebro University, Department of Clinical Research Laboratory, Faculty of Medicine and Health Halfvarson, Jonas; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health
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**Cohort profile: The Swedish Inception Cohort in inflammatory
bowel disease (SIC-IBD)**

Authors: Benita Salomon^{#1}, Olle Grännö^{#2}, Daniel Bergemalm³, Hans Strid⁴, Adam Carstens⁵⁻⁶, Henrik Hjortswang⁷, Maria Ling Lundström⁸, Jóhann P Hreinsson⁹, Sven Almer^{4, 10}, Francesca Bresso^{4,10}, Carl Eriksson³, Olof Grip¹¹, André Blomberg¹², Jan Marsal¹¹ Niloofar Nikaein¹, Shoaib Bakhtyar¹, Carl Mårten Lindqvist¹, Elisabet Hultgren Hörnquist¹, Maria K Magnusson¹³, Åsa V Keita¹⁴, Mauro D’Amato¹⁵⁻¹⁷, Dirk Repsilber¹, Lena Öhman¹³, Johan D Söderholm^{14,18}, Marie Carlson⁸, Charlotte R H Hedin^{4,10}, Robert Kruse^{1,19,20}, Jonas Halfvarson³

[#]Equally contributed and share first authorship

Affiliations

1. School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
2. Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
3. Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
4. Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden
5. Department of Internal Medicine, Ersta Hospital, Stockholm, Sweden
6. Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden.
7. Department of Gastroenterology, County Council of Östergötland, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden
8. Department of Medical Sciences, Gastroenterology Research Group, Uppsala University, Uppsala, Sweden
9. Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden
10. Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
11. Department of Gastroenterology, Skåne University Hospital, Malmö/Lund, Sweden
12. Department of Medicine, Geriatrics and Emergency Medicine, Sahlgrenska University Hospital, Östra Hospital, Gothenburg
13. Department of Microbiology and Immunology, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden
14. Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
15. Gastrointestinal Genetics Lab, CIC bioGUNE - BRTA, Derio, Spain

16. Ikerbasque, Basque Foundation for Science, Bilbao, Spain

17. Department of Medicine and Surgery, LUM University, Casamassima, Italy

18. Department of Surgery, Linköping University, Linköping, Sweden

19. Inflammatory Response and Infection Susceptibility Centre, (iRiSC), Faculty of Medicine and Health, Örebro University, Örebro, Sweden

20. Department of Clinical Research Laboratory, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Correspondence to: Jonas Halfvarson, MD, PhD, Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, SE 70182 Örebro, Sweden; Email: jonas.halfvarsson@regionorebrolan.se; Telephone number: +46 19 6021000 (switchboard)

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Abstract

Purpose: There is a need for diagnostic and prognostic biosignatures to improve long-term outcomes in inflammatory bowel disease (IBD). Here, we describe the establishment of the Swedish inception cohort in IBD (SIC-IBD) and demonstrate its potential for the identification of such signatures.

Participants: Patients aged ≥ 18 years with gastrointestinal symptoms who were referred to the gastroenterology unit due to suspected IBD at eight Swedish hospitals between November 2011 and March 2021 were eligible for inclusion.

Findings to date: In total, 368 patients with IBD (Crohn’s disease, $n=143$; ulcerative colitis, $n=201$; IBD-unclassified, $n=24$) and 168 symptomatic controls were included. In addition, 59 healthy controls without gastrointestinal symptoms were recruited as a second control group. Biospecimens and clinical data were collected at inclusion and in patients with IBD also during follow-up to 10 years. Levels of faecal calprotectin and high-sensitivity C-reactive protein were higher in patients with IBD compared to symptomatic controls and healthy controls. Preliminary results highlight the potential of serum protein signatures and autoantibodies, as well as results from faecal markers, to differentiate between IBD and symptomatic controls in the cohort. During the first year of follow-up, 36% (52/143) of the patients with Crohn's disease, 24% (49/201) with ulcerative colitis and 4% (1/24) with IBD-U experienced an aggressive disease course.

Future plans: We have established an inception cohort enabling ongoing initiatives to collect and generate clinical data and multi-omics datasets. The cohort will allow analyses for translation into candidate biosignatures to support clinical decision-making in IBD. Additionally, the data will provide insights into mechanisms of disease pathogenesis.

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Strengths and limitations

- This large, multicentre inception cohort of newly diagnosed adult IBD patients, with integrated biobanking and prospective material collection, enables exploration of IBD pathophysiology and biomarker discovery.
- The inclusion of symptomatic controls with gastrointestinal symptoms mimicking IBD but without evidence of the diagnosis provides a realistic diagnostic setting and addresses limitations of many previous cohorts.
- The use of healthy controls as a second control group offers opportunities to gain insight into IBD pathogenesis.
- The non-population-based study design and the predominance of university hospitals in recruitment may limit the generalisability of findings.
- Suboptimal sample processing at some centres, including delays in serum centrifugation and transportation of faecal samples at ambient temperatures, may have affected the quality of some specific analyses, such as microbiota analyses.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease, ulcerative colitis and IBD-unclassified (IBD-U), is a chronic disease that predominantly presents during the second and third decades of life. The disease results in an impaired quality of life for patients and substantial societal costs due to sick leave and a high use of healthcare resources [1–3]. Progressive inflammation causes damage to the gastrointestinal tract, and a substantial proportion of patients develop serious disease complications, including bowel obstruction, fistula, abscesses, and colorectal cancer [4–6].

IBD often presents with non-specific symptoms such as diarrhoea, fatigue and abdominal pain and, therefore, presents a diagnostic challenge. Commonly used biomarkers in diagnostic algorithms include C-reactive protein (CRP) and, in some regions, faecal calprotectin (FCP) which help identify patients needing referral for further investigations, including ileocolonoscopy [7]. However, the diagnostic accuracy of CRP is too low for reliably identifying IBD patients, and the utility of FCP is hampered by poor patient adherence to faecal sampling [8,9]. Furthermore, many healthcare systems do not reimburse the use of FCP for diagnostic purposes. The absence of reliable, non-invasive diagnostic biomarkers, occurrence of non-specific symptoms and limited access to ileocolonoscopy, frequently results in a significant diagnostic delay [10,11]. As a consequence, many patients have acquired considerable bowel damage (e.g., fistulas, strictures) already at diagnosis [4,11].

At diagnosis, the heterogeneity in clinical presentation and subsequent disease course make clinicians' attempts to stratify the treatment according to the individual patient's needs very difficult. While some patients experience an indolent disease course with minimal symptoms and low endoscopic activity, a substantial proportion exhibit an aggressive disease phenotype

characterised by treatment refractoriness, corticosteroid dependency, frequent hospital admissions and surgical interventions, including resection surgery and acute colectomy [12–18]. For this latter group, an early effective treatment seems advantageous, as the initial disease phase may provide a "window of opportunity" where prompt suppression of intestinal inflammation could improve long-term outcomes [19–21]. Identifying prognostic biomarkers for this group of patients is therefore critical to facilitate the timely initiation of potent treatment.

To address the need for both diagnostic and prognostic biomarkers, we established the "Swedish Inception Cohort in IBD" (SIC-IBD), a large prospective multicentre cohort involving patients with suspected IBD referred to eight hospitals in Sweden. After a comprehensive diagnostic work-up, patients were classified as incident IBD patients or symptomatic non-IBD controls, i.e., patients presenting with symptoms mimicking IBD but where IBD was ruled out. Alternative diagnoses in this patient group included infectious colitis, irritable bowel syndrome and diverticulitis. As a second control group, healthy controls without gastrointestinal symptoms were recruited. This cohort provides a rich collection of biospecimens together with detailed phenotypic characterisation collected both at diagnosis and during follow-up. Herein, we present the study design and baseline characteristics of the participants in the SIC-IBD.

COHORT DESCRIPTION

Inclusion

This longitudinal multicentre cohort study was conducted across eight Swedish hospitals: Ersta Hospital, Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Södra Älvsborg Hospital, Uppsala University Hospital, and Örebro University Hospital. Patients aged ≥ 18 years with gastrointestinal

symptoms, such as diarrhoea, abdominal pain and blood or mucus in stools, who were referred to the gastroenterology unit with suspected IBD between November 2011 and March 2021 were eligible for inclusion (Figure 1). Exclusion criteria included a previous diagnosis of Crohn's disease, ulcerative colitis or IBD unclassified, or inability to provide informed consent or to comply with protocol requirements. After obtaining written informed consent, all patients underwent a routine diagnostic work-up for IBD, following clinical practice and international guidelines [22].

Based on the diagnostic work-up, which included magnetic resonance imaging in cases where small bowel involvement was suspected, patients were classified as having incident IBD or as symptomatic controls, i.e., patients with no discernible evidence of IBD at inclusion or during follow-up. The diagnosis of IBD was based on internationally accepted clinical, endoscopic, radiological, and histological criteria [22]. Nine patients were excluded due to suspected or confirmed IBD during follow-up. Patients were followed prospectively according to clinical practice, with data collected after 3 months, 1, 3, 5, 7 and 10 years for those with IBD. In addition, a group of healthy controls, without gastrointestinal disease, was included at baseline.

168 **Demographics of patients and controls**

169 During the inclusion period, 368 patients with IBD (Crohn's disease, n=143; ulcerative colitis,
170 n=201; IBD-U, n=24) and 168 symptomatic controls were included (**Table 1**). The group of
171 symptomatic controls comprised patients who ultimately were diagnosed with various diseases,
172 including microscopic colitis, infectious enteritis, celiac disease, or irritable bowel syndrome.
173 In addition, 59 healthy controls without any history of gastrointestinal disease were recruited
174 as a second control group.

Table 1. Demographics of individuals included in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's disease n=143	Ulcerative colitis n=201	IBD-unclassified n=24	Symptomatic control n=168	Healthy control n=59
Female sex, n (%)	73 (51.1)	81 (40.3)	11 (45.8)	107 (63.7)	33 (55.9)
Median age (IQR)	28 (23-41)	34 (26-45)	33 (30-45)	34 (25-48)	26 (23-31)
Median CRP, mg/L (IQR)*	8.0 (3.3-31.8)	3.6 (1.4-8.6)	3.1 (2-5.6)	1.8 (0.9-5.9)	0.6 (0.3-1.1)
Median FCP, µg/g (IQR)*	448 (236-978)	325 (90-880)	471 (148-621)	68 (19-146)	10 (5-24)
Smoking, n (%)					
Never	70 (49)	95 (48)	12 (50)	71 (42)	41 (69)
Previous	26 (18)	59 (30)	8 (33)	29 (17)	10 (17)
Current	22 (15)	15 (7)	1 (4)	16 (10)	4 (7)
Missing	25 (17)	31 (16)	3 (12)	52 (31)	4 (7)
Median BMI, kg/m² (IQR)	23 (22-26)	24 (22-27)	27 (22-28)	26 (22-30)	23 (21-26)

*Information was missing for CRP in 62 (10%) individuals, faecal calprotectin in 217 (37%) individuals and for Body Mass Index in 198 (33%) individuals
CRP: C-reactive protein; IQR; interquartile range; FCP, faecal calprotectin

181 Healthcare setting

182 Sweden has a tax-funded universal healthcare system, and private outpatient healthcare
183 providers are few within the field of gastroenterology. In general, gastroenterologists at
184 secondary or tertiary care centres (rather than primary care) are responsible for diagnosing and
185 managing patients with IBD.

186

187 Data collection

188 *Characterisation of disease phenotype and disease activity*

189 Following informed consent, data on patient demographics, disease phenotype according to the
190 Montreal classification[23], extraintestinal manifestations, endoscopic activity (defined as the
191 presence of ulcers in Crohn's disease [yes/no] and the Mayo endoscopic subscore in ulcerative
192 colitis), IBD treatment, IBD-related surgery, and hospital admission were recorded at baseline
193 and prospectively during follow-up. Treatment-naivety was defined as no prior treatment with
194 IBD-related medications, including topical therapies. Previous treatments in patients who were
195 not treatment-naïve included mostly topical therapies but also a few days of corticosteroid
196 treatment. For healthy controls, information about basic demographics was collected. Data on
197 disease characteristics were recorded using case report forms (CRFs), and details on the
198 Montreal classification and clinical disease activity at baseline are provided in **Table 2**.

199

Table 2. Clinical characteristics of patients with Crohn’s disease, ulcerative colitis and IBD-unclassified in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's Disease n=143	Ulcerative colitis n=201	IBD-unclassified n=24
Disease location, n (%)			
ileal (L1)	48 (33)		
colonic (L2)	50 (35)		
ileocolonic (L3)	34 (24)		
upper GI (L4)	1 (1)		
unknown	10 (7)		
Disease behaviour, n (%)			
non-stricturing, non-penetrating (B1)	115 (80)		
stricturing (B2)	14 (10)		
penetrating (B3)	5 (3)		
unknown	9 (6)		
Perianal disease, n (%)			
	12 (8)		
Disease extent, n (%)			
ulcerative proctitis (E1)		64 (32)	
left-sided colitis (E2)		57 (28)	
extensive colitis (E3)		76 (38)	
unknown		4 (2)	
Treatment-naive, n (%)			
	128 (90)	185 (92)	21 (88)

Upper GI (L4) refers to patients with only upper gastrointestinal Crohn’s disease

IBD-unclassified, Inflammatory bowel disease unclassified; SIC-IBD; GI, gastrointestinal

206 *Patient-reported outcomes*

207 Patient questionnaires were employed to obtain information about clinical disease activity,
208 smoking status, recent antibiotic or non-steroid anti-inflammatory drug use, and any specific
209 dietary restrictions.

210

211 Patients were also asked to complete the Short-Health-Scale and Short Form-36 (SF-36)
212 questionnaire to obtain information about Health-Related Quality of Life (HRQoL) [24–26].
213 SF-36 is a general measure of HRQoL, whereas the Short-Health Scale is a validated measure
214 to address HRQoL in patients with IBD. It includes four dimensions: bowel symptoms, daily
215 life activities, worry and general well-being. Additional quality of life data were collected using
216 the EuroQol-5D (EQ-5D) questionnaire[27,28]. Mental health was evaluated using the Patient-
217 health Questionnaire 9 (PHQ9) [29], the Cognitive Reserve Index (CRI) [30], and the Short-
218 Form Health Survey (SF-36) [26]. Additional data on gastrointestinal symptoms was obtained
219 by using the Gastrointestinal Symptom Rating Scale (GSRS) [31] and the Rome III criteria
220 functional gastrointestinal disorders [32].

221

222 **Sample collection and biobanking**

223 Biospecimens were obtained at baseline and during follow-up, processed and biobanked
224 according to predefined standard operating procedures (SOPs). Blood samples were collected
225 in EDTA and PAX®-tubes. In addition, serum samples were obtained by centrifugation of
226 whole blood at $2400 \times g$ for 5 min at ambient temperature, followed by aliquoting of serum and
227 storing at -80°C . For six centres, blood samples were shipped unprocessed at ambient room
228 temperature and centrifuged upon arrival at the central biobank, Örebro, Sweden. The
229 participants collected faecal samples in plastic tubes at home, brought them to the hospital or

mailed them by postal service. On arrival, the samples were immediately frozen and stored at -80°C . Spot urine samples were collected during study visits, aliquoted and stored at -80°C . In addition to collecting biopsies as part of clinical routine, physicians were instructed to take intestinal biopsies from both inflamed and non-inflamed mucosa according to a predefined protocol. These biopsies were preserved in Allprotect Tissue Reagent (Qiagen, Hilden, Germany) and in a bacterial freezing medium. Biopsies in the freezing medium were immediately stored at -80°C , whereas those in Allprotect Tissue Reagent were handled according to the manufacturer's instructions. Details on the collected biological material are provided in **Table 3**.

Table 3. An overview of biospecimens collected at baseline from individuals within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

	Crohn's Disease n=143	Ulcerative colitis n=201	IBD- unclassified n=24	Symptomatic control n=168	Healthy control n=59
Serum, n (%)	138 (97)	199 (99)	23 (96)	164 (98)	59 (100)
Faecal, n (%)	62 (43)	91 (45)	9 (38)	90 (54)	58 (98)
Urine, n (%)	100 (70)	137 (68)	20 (83)	112 (67)	56 (95)
Intestinal biopsies, n (%)	93 (65)	161 (80)	18 (75)	155 (92)	58 (98)

IBD, inflammatory bowel disease

Measurements of high-sensitivity CRP and faecal calprotectin

After storage, samples for high-sensitivity (hs) CRP (serum) and calprotectin (faeces) were retrieved from the central biobank and sent to Uppsala Clinical Research Center, Uppsala, Sweden and Academic Laboratory, Department of Clinical Chemistry, University Hospital,

Uppsala, Sweden, respectively. hsCRP was assayed in a single batch for all participants at the end of the recruitment period, using a particle-enhanced immunoturbidimetric hsCRP assay (Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics) on a Roche Cobas c501. Correspondingly, FCP was extracted and analysed according to the manufacturer's instructions, with a chemiluminescent immunoassay, using the LIASON XL analyser (DiaSorin, Saluggia, Italy). Data on median levels of hsCRP and FCP across the various diagnoses are provided in **Table 1**.

Disease course outcome during follow-up

A composite outcome measure was used to categorise the disease course as aggressive or indolent during follow-up. An aggressive disease course was defined as the presence of any IBD-related surgery, hospital admission for active disease, treatment refractoriness towards targeted therapies, i.e., biologics, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators, and >two courses or high cumulative dosis of systemic corticosteroids within the first year of follow-up (**Table 4**). In addition, Crohn's disease patients with evidence of progression to a complicated disease behaviour, i.e., a new stricture, fistula, or abscess, were also categorised as having an aggressive disease course.

Table 4. Criteria for defining the disease course as aggressive or indolent within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD). Patients with any of the following events during the first year from the date of diagnosis were defined as having an aggressive disease course.

Difficulty in controlling inflammation in patients with IBD

- Hospital admission for active disease
- Surgical resection (including colectomy) or a stoma
- Use of > 2 courses of corticosteroids* or a cumulative dose of > 2.5 g equivalents of prednisolone
- Use of ≥2 targeted therapies due to poor clinical effectiveness**

Progression to complicated disease behaviour in patients with Crohn’s disease

- New fistula (recto-vaginal, enterocutaneous, internal or proctitis-related perianal fistula), or need for fistula-related surgery
- New abscess (including perianal abscess) or abscess-related surgery
- New stricture or stricture-related surgery

**A corticosteroid course was defined as an episode of treatment with specified start and stop dates. Typically, oral prednisolone was initiated at a starting dose of 40 mg once daily, with a tapering schedule of 5mg per day at weekly intervals, resulting in an 8-week treatment course. For oral budesonide courses, a fixed dose of 9 mg once daily for 8 weeks was most commonly applied.*

***Targeted therapies were defined as biologics, Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators*

282 Data management

283 Patients, physicians, or research nurses used CRFs and predefined questionnaires to collect
284 information. All data were imported after pseudonymisation into a central database with reading
285 access for all co-investigators. The database is updated every 6-12 months to allow the import
286 of new data, including follow-up visits, address possible missing information, and correct
287 potential erroneous data entries. To enable backward traceability, a data freeze is created at
288 each update. Each data freeze provides a snapshot of information contained in the database at
289 a given date.

291 Project organisation

292 The SIC-IBD represents a crucial element of the multi-modal national study to identify
293 biomarkers for diagnosis, therapy response and disease progression in IBD (BIO IBD), which
294 aims to bring leading clinicians, clinical researchers and basic scientists within the field of IBD
295 together with corporate partners. The managerial structure and the operational organisation of
296 BIO IBD are shown in **Figure 2**. An executive office has been set up at the Faculty of Health
297 and Medical Sciences, Örebro University, forming the BIO IBD Executive Committee together
298 with representatives of participating universities and university hospitals. The Executive
299 Committee coordinated the efforts of the work packages, clinical departments, biomedical
300 companies, and the Swedish patients' organisation, *Mag- och tarmförbundet* [33].

301
302 The Steering Committee, responsible for the strategic leadership, is formed by representatives
303 from involved universities, biomedical companies and the patient organisation, with equal
304 numbers of basic scientists and clinicians, equal gender, and representation of young scientists.
305 The Advisory Board, composed of internationally renowned representatives of academia and
306 the biomedical industry, provides external review and input.

Patient and Public Involvement statement

During the planning phase of the cohort study, patient representatives from the Swedish patient’s organisation, *Mag- och tarmförbundet* provided input on the study design, including the definition of the disease course during follow-up. Also, they assessed the burden of the collection of biological material and the time required for responding to the questionnaires in the study. Representatives of the patient organisation and the Swedish biomarker manufacturers in the executive committee also provided feedback during the recruitment process and follow-up of study participants. In addition to scientific reporting, key findings of the studies will be communicated to patient organisations, public health policymakers, and the public through various media and news activities. When disseminating the results, the recommendations of the International Committee of Medical Journal Editors (ICMJE) will be applied [34].

FINDINGS TO DATE

At baseline, differences in smoking habits were observed between patients with Crohn’s disease, ulcerative colitis, and IBD-U. Active smoking was more prevalent in patients with Crohn’s disease, while a higher rate of former smokers was found in patients with ulcerative colitis. While hsCRP measurements were available for 90% of all patients and controls, only 63% of patients and controls had available FCP measures in the study. An additional 44 measurements of FCP at diagnosis were available from clinical routine, but these results were excluded from this analysis due to the use of different assays. Both FCP and hsCRP levels were higher in patients with Crohn’s disease and ulcerative colitis compared to symptomatic controls and healthy controls. However, while FCP levels were significantly elevated in IBD unclassified compared to symptomatic controls, the difference in hsCRP levels between these two groups was not statistically significant. No significant differences in FCP levels were

observed between patients with Crohn's disease and ulcerative colitis, but hsCRP levels were higher in Crohn's disease patients. Significant differences in hsCRP and FCP levels were also found between symptomatic controls and healthy controls.

Preliminary results from analyses of serum proteins as well as findings from the analyses of faecal markers have highlighted the potential of these markers to differentiate between patients with IBD and symptomatic controls in this cohort, suggesting their diagnostic value [35,36]. Recent results from the analysis of anti- $\alpha\text{v}\beta 6$ autoantibodies further suggested a high diagnostic value for ulcerative colitis of this marker [37]. Additionally, preliminary data indicate differences in mucosal proteins between patients developing an aggressive course of ulcerative colitis and those with an indolent course [38].

In line with previous studies [19,39], we employed a composite outcome to characterise the disease course within the first year after diagnosis, either as aggressive or indolent (Table 4). An aggressive course was defined by treatment refractoriness, the need for surgical resection, or in the case of Crohn's disease, the development of severe complications such as strictures and fistulas. Based on this definition, 36% (52/143) of the patients with Crohn's disease, 24% (49/201) of those with ulcerative colitis, and 4.2% (1/24) with IBD-U experienced an aggressive disease course within the first year after diagnosis (**Supplementary Table 1**). These results underscore that treatment failure rates and disease complications remain unacceptably high in IBD. Aggressive disease course was associated with more extensive ulcerative colitis, while no association was found between Crohn's disease location and disease course.

STRENGTHS AND LIMITATIONS

In this large nationwide multicentre inception cohort of newly diagnosed patients with IBD, a set of highly relevant biospecimens were collected at inclusion, and patients were prospectively followed. This cohort can be used to gain insights into key pathogenic mechanisms of IBD. Moreover, it provides a valuable resource for biomarker discoveries, particularly the identification of diagnostic biomarkers for IBD and prognostic markers for future disease courses.

This cohort is one of few large-scale IBD inception cohorts of adult patients with integrated biobanking [40–42], as most of the earlier initiatives have included paediatric patients only. Most previous attempts to identify diagnostic biomarkers in inception cohorts have used healthy controls or patients with non-inflammatory conditions (e.g., irritable bowel syndrome) as a control group. These settings do not reflect a diagnostic scenario where patients with gastrointestinal symptoms that are indicative of IBD are examined. Accordingly, evaluations based on these cohorts are likely to overestimate the diagnostic capacity of potential biomarkers [43]. However, this limitation is rarely acknowledged and may partly explain why promising biomarkers fail in replication attempts and do not make their way to the clinic. To allow the identification of diagnostic biomarkers, we have included patients with symptoms indicative of IBD but without any signs of the disease at diagnostic work-up or during follow-up (symptomatic controls) as a reference group. Thus, both cases with IBD and symptomatic controls represented an unselected sample of patients who were referred to secondary care for the suspicion of IBD. In addition, we included healthy controls as a second control group to gain insight into the aetiology of IBD and to characterise pathways related to disease pathogenesis.

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3 380 In this cohort, we did not record the number of eligible patients who were not included, e.g.
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5 381 those who declined to or were not able to give informed consent or were not identified by study
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7 382 personnel. The absence of a population-based cohort design could be a limiting factor when
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10 383 interpreting associations between exposures and clinical outcomes within SIC-IBD. However,
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12 384 the proportion of IBD patients with Crohn's disease in this study (39%), the European Crohn's
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14 385 and Colitis Organization's Epidemiological Committee (EpiCom) inception cohort (37%) and
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16 386 the recent population-based Inflammatory bowel disease in South-Eastern Norway cohort III
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18 387 (35%) were similar. Likewise, the proportions of ulcerative colitis (54%, 52% and 61%) and
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20 388 IBD-U (7%, 11% and 4%) were similar in the three cohorts. Suboptimal procedures in sample
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23 389 collection further limited the study. To enable inclusion at all centres, serum samples collected
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26 390 at centres with limited sample processing capacity were shipped overnight to a central biobank
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28 391 for centrifugation and biobanking. While measured faecal markers such as calprotectin are
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30 392 stable at room temperature for several days, microbiome analyses are sensitive to pre-analytic
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33 393 sample handling [44–46].
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COLLABORATION

We have established an inception cohort of newly diagnosed adult patients with IBD, symptomatic controls and healthy controls with integrated biobanking. Initiatives are underway to generate various multi-omics data from samples collected at baseline and follow-up visits. Analyses of single and multiple datasets, including integration of clinical variables, may discover novel diagnostic and prognostic biosignatures for IBD and its subtypes. Comparisons with healthy controls may also provide insights into IBD pathogenesis and progression mechanisms. We encourage collaborations with researchers from other cohorts and case-control studies to validate findings from the SIC-IBD cohort. Also, researchers can propose new collaborative initiatives and apply for access to data and biospecimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se). All proposals will be reviewed on scientific quality and methodology by the BIOIBD executive committee.

406

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411

412 Authors' contributions

413 **Conception and design:** Jonas Halfvarson

414 **Drafting the manuscript:** Benita Salomon, Olle Grännö and Jonas Halfvarson

415 **Critical revision for intellectual content:** All authors

416 **Final approval:** All authors

417 **Accountable for all aspects of the work in ensuring that questions related to the accuracy**
418 **or integrity of any part of the work are appropriately investigated and resolved:** All
419 authors

420

421 Competing interests statement

422
423 **DB** served as a speaker and/or advisory board member for BMS, Janssen, Pfizer,
424 Pharmacosmos, Sandoz, Takeda and Tillotts Pharma. **HS** has served as speaker and/or advisory
425 board member for AbbVie Ferring, Janssen, Pfizer, Takeda, Gilead and Tillotts Pharma. **AC**
426 served as a speaker for Takeda and Ferring. **HH** has served as a speaker, consultant or advisory
427 board member for AbbVie, Ferring, Fresenius Kabi, Janssen, Norgine, Pfizer, Pharmacosmos,
428 Takeda and Tillotts and has received grant support from AbbVie, Ferring, Takeda, and Tillotts.
429 **SA** served as a member for Scientific committee/Advisory board of, Janssen, Pharmacosmos,
430 Takeda, as a consultant for Janssen, OrionPharm, Takeda, and as a speaker: Galapagos, Janssen,
431 Tillotts, received research grants from Janssen and OrionPharma. **FB** has acted as national
432 and/or local principal investigator for clinical trials for Janssen, Ferring and Abbvie. **CE**
433 received grant support/lecture fee/advisory board from Takeda, Janssen Cilag, Pfizer, Abbvie.
434 **OG** served as speaker and/or advisory board member for Abbvie, Bristol Mayer Squibb, Eli
435 Lilly, Ferring, Janssen, Pfizer Takeda, Tillotts Pharma and Vifor Pharma. **JM** has served as a

speaker, consultant or advisory board member for AbbVie, Alfasigma, Amgen, Bayer, Biogen, BMS, Eli Lilly, Ferring, Galapagos, Hospira, ITH, Janssen, Lument, MSD, Otsuka, Pfizer, Sandoz, Takeda, Tillotts and UCB; and has received grant support (not for this study) from AbbVie, BMS, Calpro AS, Carbiotix, Ferring, Fresenius Kabi, Pfizer, Svar Life Science and Takeda. **MKM** has received speaker's fees from Takeda and Janssen. **LÖ** has received a financial support for research by Genetic Analysis AS, Biocodex, Danone Research and AstraZeneca and served as Consultant/Advisory Board member for Genetic Analysis AS, and as a speaker for Biocodex, Ferring Pharmaceuticals, Takeda, AbbVie, Novartis, Janssen-Cilag and Meda. **MC** has received speaker's fees from ViforPharma. She is the national PI for clinical trials for AstraZeneca. **CRHH** has served as a speaker and/or advisory board member for AstraZeneca, Dr Falk Pharma and the Falk Foundation, Galapagos, Janssen, Pfizer, Takeda, Tillotts Pharma, and received grant support from Tillotts and Takeda. **JH** served as speaker and/or advisory board member from AbbVie, Alfasigma, Aqilion, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma and the Falk Foundation, Eli Lilly, Ferring, Galapagos, Gilead, Hospira, Index Pharma, Janssen, MEDA, Medivir, Medtronic, Merck, MSD, Novartis, Pfizer, Prometheus Laboratories Inc., Sandoz, Shire, STADA, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB and received grant support from Janssen, MSD and Takeda. The remaining authors declare no conflicts of interest.

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Ethical approval

The SIC-IBD study was approved by the Regional Ethics Committees (Dnr 2010/313). Written informed consent was obtained from all participants before inclusion.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data sharing statement

Researchers can apply for access to data and biological specimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se), including a copy of their ethics approval. All proposals will be reviewed by the BIOIBD executive committee based on scientific quality and methodology. This procedure is installed to ensure that the clinical data and biological material are being requested for scientific purposes, in accordance with the informed consent signed by the participants, as the collected data and material cannot be used by purely commercial parties. Additionally, any transfer of data or biological material must comply with Swedish law and the European Union (EU) General Data Protection Regulation (GDPR).

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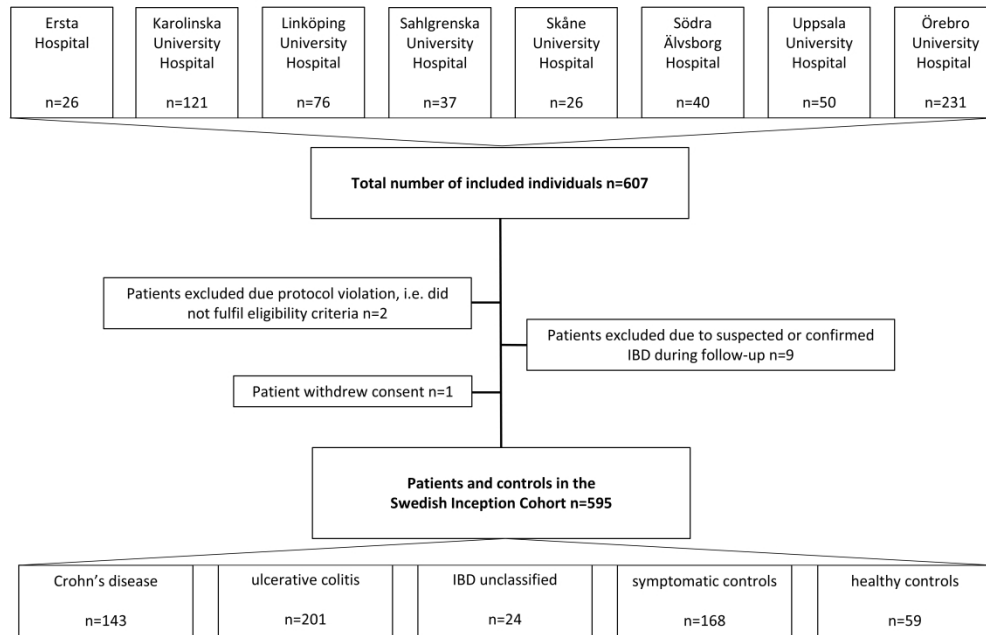


Figure 1. The flow diagram shows the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

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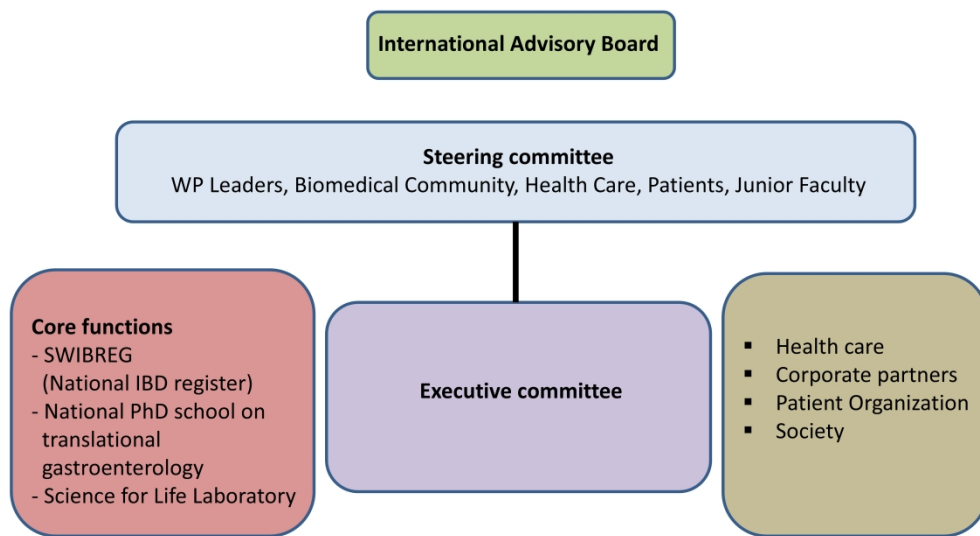


Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

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Supplementary Table 1

	Crohn's disease n=143	ulcerative colitis n=201	IBD-unclassified n=24
Aggressive disease, n (%)	52 (36.4)	45 (24.4)	1 (4.2)
Indolent disease, n (%)	79 (55.2)	140 (69.7)	22 (91.7)
Unknown*, n (%)	12 (8.4)	12 (6)	1 (4.2)

*Missing information about clinical outcomes due to incomplete follow-up during the first year after diagnosis.

BMJ Open

Cohort profile: The Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

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Complete List of Authors:	<p>Salomon, Benita; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Grännö, Olle; Örebro University, Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health Bergemalm, Daniel; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health Strid, Hans ; Karolinska Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology Carstens, Adam; Ersta Hospital, Department of Internal Medicine; Karolinska Institute, Department of Medicine Huddinge Hjortswang, Henrik; Linköping University, Department of Gastroenterology, County Council of Östergötland, Department of Clinical and Experimental Medicine Lundstrom, Maria; Uppsala University, Department of Medical Sciences, Gastroenterology Research Group Hreinsson, Johann; Sahlgrenska Academy, Department of Molecular and Clinical Medicine Almer, Sven; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology; Karolinska Institute, Department of Medicine Solna Bresso, Franscesca; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology; Karolinska Institute, Department of Medicine Solna Eriksson, Carl; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health Grip, Olof ; Skåne University Hospital Lund, Department of Gastroenterology Blomberg, André; Sahlgrenska University Hospital, Department of Medicine, Geriatrics and Emergency Medicine Marsal, Jan; Skåne University Hospital Lund, Department of Gastroenterology Nikaein, Niloofar; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Bakhtyar, Shoaib; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Lindqvist, Carl Mårten; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Hultgren-Hornquist, Elisabeth; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Magnusson, Maria; Sahlgrenska Academy, Department of Microbiology</p>

	and Immunology, Institute of Biomedicine Keita, Åsa; Linköping University, Department of Biomedical and Clinical Sciences D'Amato, Mauro ; LUM Giuseppe Degennaro University, Department of Medicine and Surgery; CIC bioGUNE, Gastrointestinal Genetics Lab; Basque Foundation for Science, Ikerbasque Repsilber, Dirk; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Öhman, Lena; Sahlgrenska Academy, Department of Microbiology and Immunology, Institute of Biomedicine Söderholm, Johan; Linköping University, Department of Biomedical and Clinical Sciences; Linköping University, Department of Surgery Carlson, Marie; Uppsala University, Department of Medical Sciences, Gastroenterology Research Group Hedin, Charlotte; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology; Karolinska Institute, Department of Medicine Solna Kruse, Robert; Örebro University, School of Medical Sciences, Faculty of Medicine and Health; Örebro University, Inflammatory Response and Infection Susceptibility Centre (iRiSC), Faculty of Medicine and Health; Örebro University, Department of Clinical Research Laboratory, Faculty of Medicine and Health Halfvarson, Jonas; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology, Diagnostics
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, GASTROENTEROLOGY, Prognosis

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1 Cohort profile: The Swedish Inception Cohort in inflammatory

2 bowel disease (SIC-IBD)

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4 **Authors:** Benita Salomon^{#1}, Olle Grännö^{#2}, Daniel Bergemalm³, Hans Strid⁴, Adam Carstens⁵⁻

5 ⁶, Henrik Hjortswang⁷, Maria Ling Lundström⁸, Jóhann P Hreinsson⁹, Sven Almer^{4, 10},

6 Francesca Bresso^{4,10}, Carl Eriksson³, Olof Grip¹¹, André Blomberg¹², Jan Marsal¹¹ Niloofar

7 Nikaein¹, Shoaib Bakhtyar¹, Carl Mårten Lindqvist¹, Elisabet Hultgren Hörnquist¹, Maria K

8 Magnusson¹³, Åsa V Keita¹⁴, Mauro D’Amato¹⁵⁻¹⁷, Dirk Repsilber¹, Lena Öhman¹³, Johan D

9 Söderholm^{14,18}, Marie Carlson⁸, Charlotte R H Hedin^{4,10}, Robert Kruse^{1,19,20}, Jonas Halfvarson³

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11 [#]Equally contributed and share first authorship

12

13 Affiliations

14 1. School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro,

15 Sweden

16 2. Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health,

17 Örebro University, Örebro, Sweden

18 3. Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro,

19 Sweden

20 4. Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and

21 Rheumatology, Karolinska University Hospital, Stockholm, Sweden

22 5. Department of Internal Medicine, Ersta Hospital, Stockholm, Sweden

23 6. Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden.

24 7. Department of Gastroenterology, County Council of Östergötland, Department of Clinical and

25 Experimental Medicine, Linköping University, Linköping, Sweden

26 8. Department of Medical Sciences, Gastroenterology Research Group, Uppsala University,

27 Uppsala, Sweden

28 9. Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of

29 Gothenburg, Göteborg, Sweden

30 10. Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

31 11. Department of Gastroenterology, Skåne University Hospital, Malmö/Lund, Sweden

32 12. Department of Medicine, Geriatrics and Emergency Medicine, Sahlgrenska University

33 Hospital, Östra Hospital, Gothenburg

34 13. Department of Microbiology and Immunology, Institute of Biomedicine, Sahlgrenska

35 Academy, University of Gothenburg, Sweden

36 14. Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

37 15. Gastrointestinal Genetics Lab, CIC bioGUNE - BRTA, Derio, Spain

16. Ikerbasque, Basque Foundation for Science, Bilbao, Spain

17. Department of Medicine and Surgery, LUM University, Casamassima, Italy

18. Department of Surgery, Linköping University, Linköping, Sweden

19. Inflammatory Response and Infection Susceptibility Centre, (iRiSC), Faculty of Medicine and Health, Örebro University, Örebro, Sweden

20. Department of Clinical Research Laboratory, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Correspondence to: Jonas Halfvarson, MD, PhD, Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, SE 70182 Örebro, Sweden; Email: jonas.halfvarsson@regionorebrolan.se; Telephone number: +46 19 6021000 (switchboard)

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Abstract

Purpose: There is a need for diagnostic and prognostic biosignatures to improve long-term outcomes in inflammatory bowel disease (IBD). Here, we describe the establishment of the Swedish inception cohort in IBD (SIC-IBD) and demonstrate its potential for the identification of such signatures.

Participants: Patients aged ≥ 18 years with gastrointestinal symptoms who were referred to the gastroenterology unit due to suspected IBD at eight Swedish hospitals between November 2011 and March 2021 were eligible for inclusion.

Findings to date: In total, 367 patients with IBD (Crohn’s disease, $n=142$; ulcerative colitis, $n=201$; IBD-unclassified, $n=24$) and 168 symptomatic controls were included. In addition, 59 healthy controls without gastrointestinal symptoms were recruited as a second control group. Biospecimens and clinical data were collected at inclusion and in patients with IBD also during follow-up to 10 years. Levels of faecal calprotectin and high-sensitivity C-reactive protein were higher in patients with IBD compared to symptomatic controls and healthy controls. Preliminary results highlight the potential of serum protein signatures and autoantibodies, as well as results from faecal markers, to differentiate between IBD and symptomatic controls in the cohort. During the first year of follow-up, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) with ulcerative colitis and 4% (1/24) with IBD-U experienced an aggressive disease course.

Future plans: We have established an inception cohort enabling ongoing initiatives to collect and generate clinical data and multi-omics datasets. The cohort will allow analyses for translation into candidate biosignatures to support clinical decision-making in IBD. Additionally, the data will provide insights into mechanisms of disease pathogenesis.

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Strengths and limitations

- This large, multicentre inception cohort of newly diagnosed adult IBD patients, with integrated biobanking and prospective material collection, enables exploration of IBD pathophysiology and biomarker discovery.
- The inclusion of symptomatic controls with gastrointestinal symptoms mimicking IBD but without evidence of the diagnosis provides a realistic diagnostic setting and addresses limitations of many previous cohorts.
- The use of healthy controls as a second control group offers opportunities to gain insight into IBD pathogenesis.
- The non-population-based study design and the predominance of university hospitals in recruitment may limit the generalisability of findings.
- Suboptimal sample processing at some centres, including delays in serum centrifugation and transportation of faecal samples at ambient temperatures, may have affected the quality of some specific analyses, such as microbiota analyses.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease, ulcerative colitis and IBD-unclassified (IBD-U), is a chronic disease that predominantly presents during the second and third decades of life. The disease results in an impaired quality of life for patients and substantial societal costs due to sick leave and a high use of healthcare resources [1–3]. Progressive inflammation causes damage to the gastrointestinal tract, and a substantial proportion of patients develop serious disease complications, including bowel obstruction, fistula, abscesses, and colorectal cancer [4–6].

IBD often presents with non-specific symptoms such as diarrhoea, fatigue and abdominal pain and, therefore, presents a diagnostic challenge. Commonly used biomarkers in diagnostic algorithms include C-reactive protein (CRP) and, in some regions, faecal calprotectin (FCP) which help identify patients needing referral for further investigations, including ileocolonoscopy [7]. However, the diagnostic accuracy of CRP is too low for reliably identifying IBD patients, and the utility of FCP is hampered by poor patient adherence to faecal sampling [8,9]. Furthermore, many healthcare systems do not reimburse the use of FCP for diagnostic purposes. The absence of reliable, non-invasive diagnostic biomarkers, occurrence of non-specific symptoms and limited access to ileocolonoscopy, frequently results in a significant diagnostic delay [10,11]. As a consequence, many patients have acquired considerable bowel damage (e.g., fistulas, strictures) already at diagnosis [4,11].

At diagnosis, the heterogeneity in clinical presentation and subsequent disease course make clinicians' attempts to stratify the treatment according to the individual patient's needs very difficult. While some patients experience an indolent disease course with minimal symptoms and low endoscopic activity, a substantial proportion exhibit an aggressive disease phenotype

characterised by treatment refractoriness, corticosteroid dependency, frequent hospital admissions and surgical interventions, including resection surgery and acute colectomy [12–18]. For this latter group, an early effective treatment seems advantageous, as the initial disease phase may provide a "window of opportunity" where prompt suppression of intestinal inflammation could improve long-term outcomes [19–21]. Identifying prognostic biomarkers for this group of patients is therefore critical to facilitate the timely initiation of potent treatment.

To address the need for both diagnostic and prognostic biomarkers, we established the "Swedish Inception Cohort in IBD" (SIC-IBD), a large prospective multicentre cohort involving patients with suspected IBD referred to eight hospitals in Sweden. After a comprehensive diagnostic work-up, patients were classified as incident IBD patients or symptomatic non-IBD controls, i.e., patients presenting with symptoms mimicking IBD but where IBD was ruled out. Alternative diagnoses in this patient group included infectious colitis, irritable bowel syndrome and diverticulitis. As a second control group, healthy controls without gastrointestinal symptoms were recruited. This cohort provides a rich collection of biospecimens together with detailed phenotypic characterisation collected both at diagnosis and during follow-up. Herein, we present the study design and baseline characteristics of the participants in the SIC-IBD.

COHORT DESCRIPTION

Inclusion

This longitudinal multicentre cohort study was conducted across eight Swedish hospitals: Ersta Hospital, Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Södra Älvsborg Hospital, Uppsala University Hospital, and Örebro University Hospital. Patients aged ≥ 18 years with gastrointestinal

symptoms, such as diarrhoea, abdominal pain and blood or mucus in stools, who were referred to the gastroenterology unit with suspected IBD between November 2011 and March 2021 were eligible for inclusion (Figure 1). Exclusion criteria included a previous diagnosis of Crohn's disease, ulcerative colitis or IBD unclassified, or inability to provide informed consent or to comply with protocol requirements. After obtaining written informed consent, all patients underwent a routine diagnostic work-up for IBD, following clinical practice and international guidelines [22].

Based on the diagnostic work-up, which included magnetic resonance imaging in cases where small bowel involvement was suspected, patients were classified as having incident IBD or as symptomatic controls, i.e., patients with no discernible evidence of IBD at inclusion or during follow-up. The diagnosis of IBD was based on internationally accepted clinical, endoscopic, radiological, and histological criteria [22]. Nine patients were excluded due to suspected or confirmed IBD during follow-up. Patients were followed prospectively according to clinical practice, with data collected after 3 months, 1, 3, 5, 7 and 10 years for those with IBD. In addition, a group of healthy controls, without gastrointestinal disease, was included at baseline.

168 **Demographics of patients and controls**

169 During the inclusion period, 367 patients with IBD (Crohn's disease, n=142; ulcerative colitis,
170 n=201; IBD-U, n=24) and 168 symptomatic controls were included (**Table 1**). The group of
171 symptomatic controls comprised patients who ultimately were diagnosed with various diseases,
172 including microscopic colitis, infectious enteritis, celiac disease, or irritable bowel syndrome.
173 In addition, 59 healthy controls without any history of gastrointestinal disease were recruited
174 as a second control group.

Table 1. Demographics of individuals included in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's disease n=142	Ulcerative colitis n=201	IBD-unclassified n=24	Symptomatic control n=168	Healthy control n=59
Female sex, n (%)	72 (50.7)	81 (40.3)	11 (45.8)	107 (63.7)	33 (55.9)
Median age (IQR)	28 (23-41)	34 (26-45)	33 (30-45)	34 (25-48)	26 (23-31)
Median CRP, mg/L (IQR)*	8.0 (3.2-32.3)	3.7 (1.4-8.7)	3.1 (2-5.6)	1.8 (0.9-5.9)	0.6 (0.3-1.1)
Median FCP, µg/g (IQR)*	452 (234-981)	325 (90-880)	471 (148-621)	68 (19-146)	10 (5-24)
Smoking, n (%)					
Never	81 (57)	104 (52)	13 (54)	76 (45)	43 (73)
Previous	28 (20)	64 (32)	8 (33)	30 (18)	10 (17)
Current	25 (18)	16 (8)	2 (8)	18 (11)	4 (7)
Missing	8 (6)	17 (8)	1 (4)	44 (26)	2 (3)
Median BMI, kg/m² (IQR)	23 (21-26)	24 (22-27)	27 (22-28)	26 (22-30)	23 (21-25)

*Information was missing for CRP in 62 (10%) individuals, faecal calprotectin in 217 (37%) individuals and for Body Mass Index in 197 (33%) individuals
CRP: C-reactive protein; IQR; interquartile range; FCP, faecal calprotectin

181 Healthcare setting

182 Sweden has a tax-funded universal healthcare system, and private outpatient healthcare
183 providers are few within the field of gastroenterology. In general, gastroenterologists at
184 secondary or tertiary care centres (rather than primary care) are responsible for diagnosing and
185 managing patients with IBD.

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187 Data collection

188 *Characterisation of disease phenotype and disease activity*

189 Following informed consent, data on patient demographics, disease phenotype according to the
190 Montreal classification[23], extraintestinal manifestations, endoscopic activity (defined as the
191 presence of ulcers in Crohn's disease [yes/no] and the Mayo endoscopic subscore in ulcerative
192 colitis), IBD treatment, IBD-related surgery, and hospital admission were recorded at baseline
193 and prospectively during follow-up. Treatment-naivety was defined as no prior treatment with
194 IBD-related medications, including topical therapies. Previous treatments in patients who were
195 not treatment-naïve included mostly topical therapies but also a few days of corticosteroid
196 treatment. For healthy controls, information about basic demographics was collected. Data on
197 disease characteristics were recorded using case report forms (CRFs), and details on the
198 Montreal classification and clinical disease activity at baseline are provided in **Table 2**.

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Table 2. Clinical characteristics of patients with Crohn’s disease, ulcerative colitis and IBD-
unclassified in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24
Disease location, n (%)			
ileal (L1)	48 (34)		
colonic (L2)	50 (35)		
ileocolonic (L3)	34 (24)		
upper GI (L4)	1 (1)		
unknown	9 (6)		
Disease behaviour, n (%)			
non-stricturing, non-penetrating (B1)	115 (80)		
stricturing (B2)	14 (10)		
penetrating (B3)	5 (3)		
unknown	8 (6)		
Perianal disease, n (%)			
	12 (8)		
Disease extent, n (%)			
ulcerative proctitis (E1)		64 (32)	
left-sided colitis (E2)		57 (28)	
extensive colitis (E3)		76 (38)	
unknown		4 (2)	
Treatment-naïve, n (%)			
	128 (90)	185 (92)	21 (88)

Upper GI (L4) refers to patients with only upper gastrointestinal Crohn’s disease
IBD-unclassified, Inflammatory bowel disease unclassified; SIC-IBD; GI, gastrointestinal

206 *Patient-reported outcomes*

207 Patient questionnaires were employed to obtain information about clinical disease activity,
208 smoking status, recent antibiotic or non-steroid anti-inflammatory drug use, and any specific
209 dietary restrictions.

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211 Patients were also asked to complete the Short-Health-Scale and Short Form-36 (SF-36)
212 questionnaire to obtain information about Health-Related Quality of Life (HRQoL) [24–26].
213 SF-36 is a general measure of HRQoL, whereas the Short-Health Scale is a validated measure
214 to address HRQoL in patients with IBD. It includes four dimensions: bowel symptoms, daily
215 life activities, worry and general well-being. Additional quality of life data were collected using
216 the EuroQol-5D (EQ-5D) questionnaire [27,28]. Mental health was evaluated using the Patient-
217 health Questionnaire 9 (PHQ9) [29], the Cognitive Reserve Index (CRI) [30], and the Short-
218 Form Health Survey (SF-36) [26]. Additional data on gastrointestinal symptoms was obtained
219 by using the Gastrointestinal Symptom Rating Scale (GSRS) [31] and the Rome III criteria
220 functional gastrointestinal disorders [32].

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222 **Sample collection and biobanking**

223 Biospecimens were obtained at baseline and during follow-up, processed and biobanked
224 according to predefined standard operating procedures (SOPs). Blood samples were collected
225 in EDTA and PAX®-tubes. In addition, serum samples were obtained by centrifugation of
226 whole blood at $2400 \times g$ for 5 min at ambient temperature, followed by aliquoting of serum and
227 storing at -80°C . For six centres, blood samples were shipped unprocessed at ambient room
228 temperature and centrifuged upon arrival at the central biobank, Örebro, Sweden. The
229 participants collected faecal samples in plastic tubes at home, brought them to the hospital or

mailed them by postal service. On arrival, the samples were immediately frozen and stored at -80°C . Spot urine samples were collected during study visits, aliquoted and stored at -80°C . In addition to collecting biopsies as part of clinical routine, physicians were instructed to take intestinal biopsies from both inflamed and non-inflamed mucosa according to a predefined protocol. These biopsies were preserved in Allprotect Tissue Reagent (Qiagen, Hilden, Germany) and in a bacterial freezing medium. Biopsies in the freezing medium were immediately stored at -80°C , whereas those in Allprotect Tissue Reagent were handled according to the manufacturer's instructions. Details on the collected biological material are provided in **Table 3**.

Table 3. An overview of biospecimens collected at baseline from individuals within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24	Symptoma tic control n=168	Healthy control n=59
Serum, n (%)	137 (96)	199 (99)	23 (96)	164 (98)	59 (100)
Faecal, n (%)*	99 (70)	137 (68)	20 (83)	112 (67)	56 (95)
Intestinal biopsies, n (%)	92 (65)	161 (80)	18 (75)	155 (92)	58 (98)
Urine, n (%)	62 (44)	91 (45)	9 (38)	90 (54)	58 (98)

*Faecal samples for microbiome analyses and for additional faecal marker. Samples for faecal calprotectin were handled separately.
IBD, inflammatory bowel disease

Measurements of high-sensitivity CRP and faecal calprotectin

After storage, samples for high-sensitivity (hs) CRP (serum) and calprotectin (faeces) were retrieved from the central biobank and sent to Uppsala Clinical Research Center, Uppsala, Sweden and Academic Laboratory, Department of Clinical Chemistry, University Hospital,

Uppsala, Sweden, respectively. hsCRP was assayed in a single batch for all participants at the end of the recruitment period, using a particle-enhanced immunoturbidimetric hsCRP assay (Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics) on a Roche Cobas c501. Correspondingly, FCP was extracted and analysed according to the manufacturer's instructions, with a chemiluminescent immunoassay, using the LIASON XL analyser (DiaSorin, Saluggia, Italy). Data on median levels of hsCRP and FCP across the various diagnoses are provided in **Table 1**.

Disease course outcome during follow-up

A composite outcome measure was used to categorise the disease course as aggressive or indolent during follow-up. An aggressive disease course was defined as the presence of any IBD-related surgery, hospital admission for active disease, treatment refractoriness towards targeted therapies, i.e., biologics, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators, and >two courses or high cumulative dosis of systemic corticosteroids within the first year of follow-up (**Table 4**). In addition, Crohn's disease patients with evidence of progression to a complicated disease behaviour, i.e., a new stricture, fistula, or abscess, were also categorised as having an aggressive disease course.

Table 4. Criteria for defining the disease course as aggressive or indolent within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD). Patients with any of the following events during the first year from the date of diagnosis were defined as having an aggressive disease course.

Difficulty in controlling inflammation in patients with IBD

- Hospital admission for active disease
- Surgical resection (including colectomy) or a stoma
- Use of > 2 courses of corticosteroids* or a cumulative dose of > 2.5 g equivalents of prednisolone
- Use of ≥2 targeted therapies due to poor clinical effectiveness**

Progression to complicated disease behaviour in patients with Crohn’s disease

- New fistula (recto-vaginal, enterocutaneous, internal or proctitis-related perianal fistula), or need for fistula-related surgery
- New abscess (including perianal abscess) or abscess-related surgery
- New stricture or stricture-related surgery

**A corticosteroid course was defined as an episode of treatment with specified start and stop dates. Typically, oral prednisolone was initiated at a starting dose of 40 mg once daily, with a tapering schedule of 5mg per day at weekly intervals, resulting in an 8-week treatment course. For oral budesonide courses, a fixed dose of 9 mg once daily for 8 weeks was most commonly applied.*

***Targeted therapies were defined as biologics, Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators*

284 **Data management**

285 Patients, physicians, or research nurses used CRFs and predefined questionnaires to collect
286 information. All data were imported after pseudonymisation into a central database with reading
287 access for all co-investigators. The database is updated every 6-12 months to allow the import
288 of new data, including follow-up visits, address possible missing information, and correct
289 potential erroneous data entries. To enable backward traceability, a data freeze is created at
290 each update. Each data freeze provides a snapshot of information contained in the database at
291 a given date.

293 **Project organisation**

294 The SIC-IBD represents a crucial element of the multi-modal national study to identify
295 biomarkers for diagnosis, therapy response and disease progression in IBD (BIO IBD), which
296 aims to bring leading clinicians, clinical researchers and basic scientists within the field of IBD
297 together with corporate partners. The managerial structure and the operational organisation of
298 BIO IBD are shown in **Figure 2**. An executive office has been set up at the Faculty of Health
299 and Medical Sciences, Örebro University, forming the BIO IBD Executive Committee together
300 with representatives of participating universities and university hospitals. The Executive
301 Committee coordinated the efforts of the work packages, clinical departments, biomedical
302 companies, and the Swedish patients' organisation, *Mag- och tarmförbundet* [33].

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304 The Steering Committee, responsible for the strategic leadership, is formed by representatives
305 from involved universities, biomedical companies and the patient organisation, with equal
306 numbers of basic scientists and clinicians, equal gender, and representation of young scientists.
307 The Advisory Board, composed of internationally renowned representatives of academia and
308 the biomedical industry, provides external review and input.

Patient and Public Involvement statement

During the planning phase of the cohort study, patient representatives from the Swedish patient’s organisation, *Mag- och tarmförbundet* provided input on the study design, including the definition of the disease course during follow-up. Also, they assessed the burden of the collection of biological material and the time required for responding to the questionnaires in the study. Representatives of the patient organisation and the Swedish biomarker manufacturers in the executive committee also provided feedback during the recruitment process and follow-up of study participants. In addition to scientific reporting, key findings of the studies will be communicated to patient organisations, public health policymakers, and the public through various media and news activities. When disseminating the results, the recommendations of the International Committee of Medical Journal Editors (ICMJE) will be applied [34].

FINDINGS TO DATE

At baseline, differences in smoking habits were observed between patients with Crohn’s disease and ulcerative colitis. Active smoking was more prevalent in patients with Crohn’s disease, while a higher rate of former smokers was found in patients with ulcerative colitis. While hsCRP measurements were available for 90% of all patients and controls, only 63% of patients and controls had available FCP measures in the study. An additional 44 measurements of FCP at diagnosis were available from clinical routine, but these results were excluded from this analysis due to the use of different assays. Both FCP and hsCRP levels were higher in patients with Crohn’s disease and ulcerative colitis compared to symptomatic controls and healthy controls. However, while FCP levels were significantly elevated in IBD unclassified compared to symptomatic controls, the difference in hsCRP levels between these two groups was not statistically significant. No significant differences in FCP levels were observed between

patients with Crohn's disease and ulcerative colitis, but hsCRP levels were higher in Crohn's disease patients. Significant differences in hsCRP and FCP levels were also found between symptomatic controls and healthy controls.

Preliminary results from analyses of serum proteins as well as findings from the analyses of faecal markers have highlighted the potential of these markers to differentiate between patients with IBD and symptomatic controls in this cohort, suggesting their diagnostic value [35,36]. Recent results from the analysis of anti- $\alpha\beta 6$ autoantibodies further suggested a high diagnostic value for ulcerative colitis of this marker [37]. Additionally, preliminary data indicate differences in mucosal proteins between patients developing an aggressive course of ulcerative colitis and those with an indolent course [38].

In line with previous studies [19,39], we employed a composite outcome to characterise the disease course within the first year after diagnosis, either as aggressive or indolent (Table 4). An aggressive course was defined by treatment refractoriness, the need for surgical resection, or in the case of Crohn's disease, the development of severe complications such as strictures and fistulas. Based on this definition, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) of those with ulcerative colitis, and 4% (1/24) with IBD-U experienced an aggressive disease course within the first year after diagnosis (**Supplementary Table 1**). These results underscore that treatment failure rates and disease complications remain unacceptably high in IBD. Aggressive disease course was associated with more extensive ulcerative colitis, while no association was found between Crohn's disease location and disease course.

STRENGTHS AND LIMITATIONS

In this large nationwide multicentre inception cohort of newly diagnosed patients with IBD, a set of highly relevant biospecimens were collected at inclusion, and patients were prospectively followed. This cohort can be used to gain insights into key pathogenic mechanisms of IBD. Moreover, it provides a valuable resource for biomarker discoveries, particularly the identification of diagnostic biomarkers for IBD and prognostic markers for future disease courses.

This cohort is one of few large-scale IBD inception cohorts of adult patients with integrated biobanking [40–42], as most of the earlier initiatives have included paediatric patients only. Most previous attempts to identify diagnostic biomarkers in inception cohorts have used healthy controls or patients with non-inflammatory conditions (e.g., irritable bowel syndrome) as a control group. These settings do not reflect a diagnostic scenario where patients with gastrointestinal symptoms that are indicative of IBD are examined. Accordingly, evaluations based on these cohorts are likely to overestimate the diagnostic capacity of potential biomarkers [43]. However, this limitation is rarely acknowledged and may partly explain why promising biomarkers fail in replication attempts and do not make their way to the clinic. To allow the identification of diagnostic biomarkers, we have included patients with symptoms indicative of IBD but without any signs of the disease at diagnostic work-up or during follow-up (symptomatic controls) as a reference group. Thus, both cases with IBD and symptomatic controls represented an unselected sample of patients who were referred to secondary care for the suspicion of IBD. In addition, we included healthy controls as a second control group to gain insight into the aetiology of IBD and to characterise pathways related to disease pathogenesis.

A composite outcome was chosen to categorise disease course since no established gold standard for defining or classifying IBD course currently exists. The Montreal classification provides a framework for Crohn's disease location and behaviour, and extent of ulcerative colitis but does not capture disease progression over time [23]. Several other cohorts, including the European Crohn's and Colitis Organization's Epidemiological Committee (EpiCom) inception cohort [14] and Inflammatory bowel disease in South-Eastern Norway cohort III (IBSEN III) [41], have recorded disease-related events such as IBD-related surgery, disease complications, and hospital admissions to assess disease severity over time. Similarly, the Randomised Evaluation of an Algorithm for Crohn's Treatment (REACT) [19] and REACT-2 [39] trials employed a composite outcome to define disease course in Crohn's disease using similar criteria. While a single criterion, such as treatment escalation or new disease complications in Crohn's disease [44,45], may facilitate interpretability, a composite outcome allows a more comprehensive assessment of disease severity over time. This approach captures multiple dimensions, including difficulties in controlling inflammation, fibrosis-related complications, and poor treatment response, thereby offering a broader perspective on disease course.

In this cohort, we did not record the number of eligible patients who were not included, e.g. those who declined to or were not able to give informed consent or were not identified by study personnel. The absence of a population-based cohort design could be a limiting factor when interpreting associations between exposures and clinical outcomes within SIC-IBD, as selection bias may have been introduced. However, the proportion of IBD patients with Crohn's disease in this study (39%), the EpiCom inception cohort (37%) and the recent population-based Inflammatory bowel disease in South-Eastern Norway cohort III (35%) were similar. Likewise, the proportions of ulcerative colitis (55%, 52% and 61%) and IBD-U (7%, 11% and 4%) were

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similar in the three cohorts. Suboptimal procedures in sample collection further limited the study. To enable inclusion at all centres, serum samples collected at centres with limited sample processing capacity were shipped overnight to a central biobank for centrifugation and biobanking. While measured faecal markers such as calprotectin are stable at room temperature for several days, microbiome analyses are sensitive to pre-analytic sample handling [46–48]. Furthermore, not all included patients were treatment-naïve, which could influence the molecular data and may warrant sensitivity analyses. Approximately 9% of patients had initiated treatment before inclusion, most commonly with one or a few doses of corticosteroids in the days preceding inclusion.

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COLLABORATION

We have established an inception cohort of newly diagnosed adult patients with IBD, symptomatic controls and healthy controls with integrated biobanking. Initiatives are underway to generate various multi-omics data from samples collected at baseline and follow-up visits. Analyses of single and multiple datasets, including integration of clinical variables, may discover novel diagnostic and prognostic biosignatures for IBD and its subtypes. Comparisons with healthy controls may also provide insights into IBD pathogenesis and progression mechanisms. We encourage collaborations with researchers from other cohorts and case-control studies to validate findings from the SIC-IBD cohort. Also, researchers can propose new collaborative initiatives and apply for access to data and biospecimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se). All proposals will be reviewed on scientific quality and methodology by the BIOIBD executive committee.

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433 **Authors' contributions**

434 **Conception and design:** Jonas Halfvarson

435 **Drafting the manuscript:** Benita Salomon, Olle Grännö and Jonas Halfvarson

436 **Critical revision for intellectual content:** All authors

437 **Final approval:** All authors

438 **Accountable for all aspects of the work in ensuring that questions related to the accuracy**

439 **or integrity of any part of the work are appropriately investigated and resolved:** All

440 authors

441 **Guarantor:** Jonas Halfvarson

442

443 **Competing interests statement**

444

445 **DB** served as a speaker and/or advisory board member for Abbvie, BMS, Johnson and Johnson,

446 Pfizer, Pharmacosmos, Sandoz, Takeda and Tillotts Pharma. **HS** has served as speaker and/or

447 advisory board member for AbbVie Ferring, Janssen, Pfizer, Takeda, Gilead and Tillotts

448 Pharma. **AC** served as a speaker for Takeda and Ferring. **HH** has served as a speaker, consultant

449 or advisory board member for AbbVie, Ferring, Fresenius Kabi, Janssen, Norgine, Pfizer,

450 Pharmacosmos, Takeda and Tillotts and has received grant support from AbbVie, Ferring,

451 Takeda, and Tillotts. **SA** served as a member for Scientific committee/Advisory board of,

452 Janssen, Pharmacosmos, Takeda, as a consultant for Janssen, OrionPharm, Takeda, and as a

453 speaker: Galapagos, Janssen, Tillotts, received research grants from Janssen and OrionPharma.

454 **FB** has acted as national and/or local principal investigator for clinical trials for Janssen, Ferring

455 and Abbvie. **CE** received grant support/lecture fee/advisory board from Takeda, Janssen Cilag,

456 Pfizer, Abbvie. **OG** served as speaker and/or advisory board member for Abbvie, Bristol Mayer

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Ethical approval

The SIC-IBD study was approved by the Regional Ethics Committees (Dnr 2010/313). Written informed consent was obtained from all participants before inclusion.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data sharing statement

Researchers can apply for access to data and biological specimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se), including a copy of their ethics approval. All proposals will be reviewed by the BIOIBD executive committee based on scientific quality and methodology. This procedure is installed to ensure that the clinical data and biological material are being requested for scientific purposes, in accordance with the informed consent signed by the participants, as the collected data and material cannot be used by purely commercial parties. Additionally, any transfer of data or biological material must comply with Swedish law and the European Union (EU) General Data Protection Regulation (GDPR).

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646 Figure 1. The flow diagram shows the number of included individuals at each hospital, the
647 number of patients excluded and the final number of patients and controls in the Swedish
648 Inception Cohort in inflammatory bowel disease (SIC-IBD).

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650 Figure 2. Managerial structure and the operational organisation of the multi-modal national
651 study to identify biomarkers for diagnosis, therapy response and disease progression in
652 inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-
653 IBD) represents an important resource.

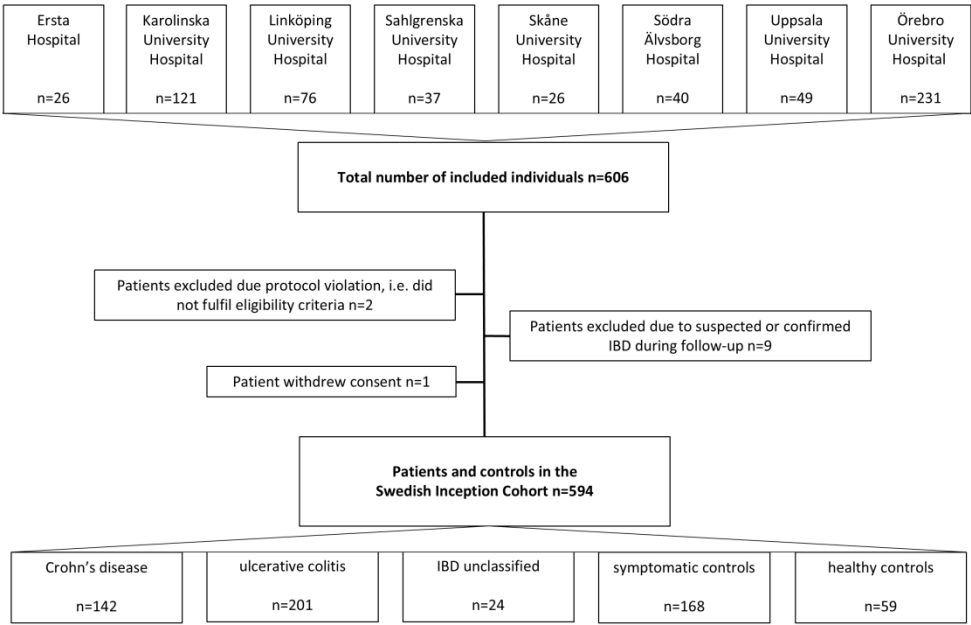


Figure 1. The flow diagram shows the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

609x395mm (118 x 118 DPI)

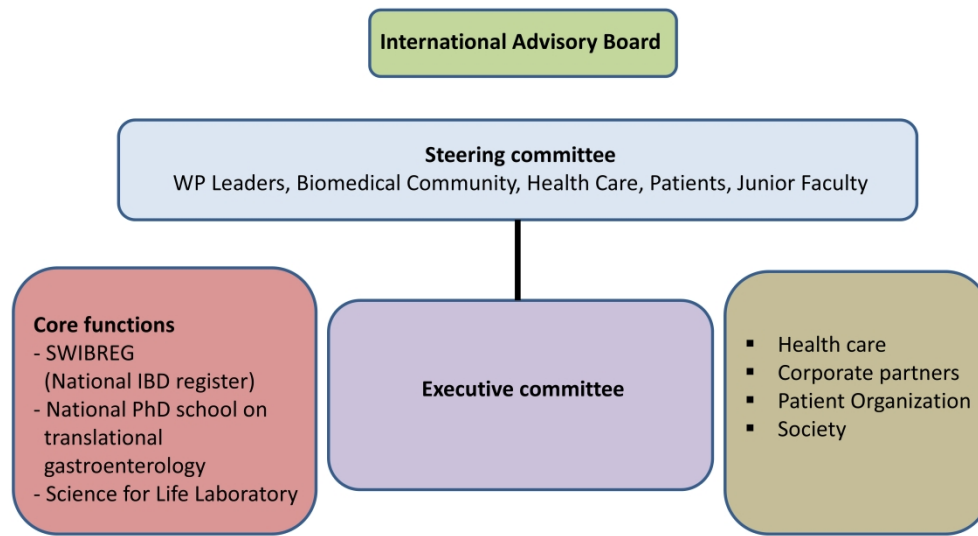


Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

611x334mm (236 x 236 DPI)

Supplementary Table 1

	Crohn's disease n=142	ulcerative colitis n=201	IBD-unclassified n=24
Aggressive disease, n (%)	53 (37.3)	48 (23.9)	1 (4.2)
Indolent disease, n (%)	83 (58.5)	144 (71.6)	22 (91.7)
Unknown*, n (%)	6 (4.2)	9 (4.5)	1 (4.2)

*Missing information about clinical outcomes due to incomplete follow-up during the first year after diagnosis.

BMJ Open

Cohort profile: The Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

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Complete List of Authors:	<p>Salomon, Benita; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Grännö, Olle; Örebro University, Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health Bergemalm, Daniel; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health Strid, Hans ; Karolinska Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology Carstens, Adam; Ersta Hospital, Department of Internal Medicine; Karolinska Institute, Department of Medicine Huddinge Hjortswang, Henrik; Linköping University, Department of Gastroenterology, County Council of Östergötland, Department of Clinical and Experimental Medicine Lundstrom, Maria; Uppsala University, Department of Medical Sciences, Gastroenterology Research Group Hreinsson, Johann; Sahlgrenska Academy, Department of Molecular and Clinical Medicine Almer, Sven; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology; Karolinska Institute, Department of Medicine Solna Bresso, Franscesca; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology; Karolinska Institute, Department of Medicine Solna Eriksson, Carl; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health Grip, Olof ; Skåne University Hospital Lund, Department of Gastroenterology Blomberg, André; Sahlgrenska University Hospital, Department of Medicine, Geriatrics and Emergency Medicine Marsal, Jan; Skåne University Hospital Lund, Department of Gastroenterology Nikaein, Niloofar; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Bakhtyar, Shoaib; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Lindqvist, Carl Mårten; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Hultgren-Hornquist, Elisabeth; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Magnusson, Maria; Sahlgrenska Academy, Department of Microbiology</p>

	and Immunology, Institute of Biomedicine Keita, Åsa; Linköping University, Department of Biomedical and Clinical Sciences D'Amato, Mauro ; LUM Giuseppe Degennaro University, Department of Medicine and Surgery; CIC bioGUNE, Gastrointestinal Genetics Lab; Basque Foundation for Science, Ikerbasque Repsilber, Dirk; Örebro University, School of Medical Sciences, Faculty of Medicine and Health Öhman, Lena; Sahlgrenska Academy, Department of Microbiology and Immunology, Institute of Biomedicine Söderholm, Johan; Linköping University, Department of Biomedical and Clinical Sciences; Linköping University, Department of Surgery Carlson, Marie; Uppsala University, Department of Medical Sciences, Gastroenterology Research Group Hedin, Charlotte; Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology; Karolinska Institute, Department of Medicine Solna Kruse, Robert; Örebro University, School of Medical Sciences, Faculty of Medicine and Health; Örebro University, Inflammatory Response and Infection Susceptibility Centre (iRiSC), Faculty of Medicine and Health; Örebro University, Department of Clinical Research Laboratory, Faculty of Medicine and Health Halfvarson, Jonas; Örebro University, Department of Gastroenterology, Faculty of Medicine and Health
Primary Subject Heading:	Gastroenterology and hepatology
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Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, GASTROENTEROLOGY, Prognosis

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1 Cohort profile: The Swedish Inception Cohort in inflammatory

2 bowel disease (SIC-IBD)

3

4 Benita Salomon^{#1}, Olle Grännö^{#2}, Daniel Bergemalm³, Hans Strid⁴, Adam Carstens⁵⁻⁶, Henrik

5 Hjortswang⁷, Maria Ling Lundström⁸, Jóhann P Hreinsson⁹, Sven Almer^{4, 10}, Francesca

6 Bresso^{4,10}, Carl Eriksson³, Olof Grip¹¹, André Blomberg¹², Jan Marsal¹¹ Niloofar Nikaein¹,

7 Shoaib Bakhtyar¹, Carl Mårten Lindqvist¹, Elisabet Hultgren Hörnquist¹, Maria K

8 Magnusson¹³, Åsa V Keita¹⁴, Mauro D'Amato¹⁵⁻¹⁷, Dirk Repsilber¹, Lena Öhman¹³, Johan D

9 Söderholm^{14,18}, Marie Carlson⁸, Charlotte R H Hedin^{4,10}, Robert Kruse^{1,19,20}, Jonas Halfvarson³

10

11 #Contributed equally and share first authorship

12

13 Affiliations

14 1. School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro,

15 Sweden

16 2. Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health,

17 Örebro University, Örebro, Sweden

18 3. Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro,

19 Sweden

20 4. Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and

21 Rheumatology, Karolinska University Hospital, Stockholm, Sweden

22 5. Department of Internal Medicine, Ersta Hospital, Stockholm, Sweden

23 6. Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden.

24 7. Department of Gastroenterology, County Council of Östergötland, Department of Clinical and

25 Experimental Medicine, Linköping University, Linköping, Sweden

26 8. Department of Medical Sciences, Gastroenterology Research Group, Uppsala University,

27 Uppsala, Sweden

28 9. Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of

29 Gothenburg, Göteborg, Sweden

30 10. Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

31 11. Department of Gastroenterology, Skåne University Hospital, Malmö/Lund, Sweden

32 12. Department of Medicine, Geriatrics and Emergency Medicine, Sahlgrenska University

33 Hospital, Östra Hospital, Gothenburg

34 13. Department of Microbiology and Immunology, Institute of Biomedicine, Sahlgrenska

35 Academy, University of Gothenburg, Sweden

36 14. Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

37 15. Gastrointestinal Genetics Lab, CIC bioGUNE - BRTA, Derio, Spain

16. Ikerbasque, Basque Foundation for Science, Bilbao, Spain

17. Department of Medicine and Surgery, LUM University, Casamassima, Italy

18. Department of Surgery, Linköping University, Linköping, Sweden

19. Inflammatory Response and Infection Susceptibility Centre, (iRiSC), Faculty of Medicine and Health, Örebro University, Örebro, Sweden

20. Department of Clinical Research Laboratory, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Correspondence to:

Jonas Halfvarson, MD, PhD, Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, SE 70182 Örebro, Sweden
Email: jonas.halfvarsson@regionorebrolan.se

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Abstract

Purpose: There is a need for diagnostic and prognostic biosignatures to improve long-term outcomes in inflammatory bowel disease (IBD). Here, we describe the establishment of the Swedish inception cohort in IBD (SIC-IBD) and demonstrate its potential for the identification of such signatures.

Participants: Patients aged ≥ 18 years with gastrointestinal symptoms who were referred to the gastroenterology unit due to suspected IBD at eight Swedish hospitals between November 2011 and March 2021 were eligible for inclusion.

Findings to date: In total, 367 patients with IBD (Crohn’s disease, n=142; ulcerative colitis, n=201; IBD-unclassified, n=24) and 168 symptomatic controls were included. In addition, 59 healthy controls without gastrointestinal symptoms were recruited as a second control group. Biospecimens and clinical data were collected at inclusion and in patients with IBD also during follow-up to 10 years. Levels of faecal calprotectin and high-sensitivity C-reactive protein were higher in patients with IBD compared to symptomatic controls and healthy controls. Preliminary results highlight the potential of serum protein signatures and autoantibodies, as well as results from faecal markers, to differentiate between IBD and symptomatic controls in the cohort. During the first year of follow-up, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) with ulcerative colitis and 4% (1/24) with IBD-U experienced an aggressive disease course.

Future plans: We have established an inception cohort enabling ongoing initiatives to collect and generate clinical data and multi-omics datasets. The cohort will allow analyses for translation into candidate biosignatures to support clinical decision-making in IBD. Additionally, the data will provide insights into mechanisms of disease pathogenesis.

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Strengths and limitations of this study

- This large, multicentre inception cohort of newly diagnosed adult patients with inflammatory bowel disease (IBD), with integrated biobanking and prospective material collection, enables exploration of IBD pathophysiology and biomarker discovery.
- The inclusion of symptomatic controls with gastrointestinal symptoms mimicking IBD but without evidence of the diagnosis provides a realistic diagnostic setting and addresses limitations of many previous cohorts.
- The use of healthy controls as a second control group offers opportunities to gain insight into IBD pathogenesis.
- The non-population-based study design and the predominance of university hospitals in recruitment may limit the generalisability of findings.
- Suboptimal sample processing at some centres, including delays in serum centrifugation and transportation of faecal samples at ambient temperatures, may have affected the quality of some specific analyses, such as microbiota analyses.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease, ulcerative colitis and IBD-unclassified (IBD-U), is a chronic disease that predominantly presents during the second and third decades of life. The disease results in an impaired quality of life for patients and substantial societal costs due to sick leave and a high use of healthcare resources [1–3]. Progressive inflammation causes damage to the gastrointestinal tract, and a substantial proportion of patients develop serious disease complications, including bowel obstruction, fistula, abscesses, and colorectal cancer [4–6].

IBD often presents with non-specific symptoms such as diarrhoea, fatigue and abdominal pain and, therefore, presents a diagnostic challenge. Commonly used biomarkers in diagnostic algorithms include C-reactive protein (CRP) and, in some regions, faecal calprotectin (FCP) which help identify patients needing referral for further investigations, including ileocolonoscopy [7]. However, the diagnostic accuracy of CRP is too low for reliably identifying IBD patients, and the utility of FCP is hampered by poor patient adherence to faecal sampling [8,9]. Furthermore, many healthcare systems do not reimburse the use of FCP for diagnostic purposes. The absence of reliable, non-invasive diagnostic biomarkers, occurrence of non-specific symptoms and limited access to ileocolonoscopy, frequently results in a significant diagnostic delay [10,11]. As a consequence, many patients have acquired considerable bowel damage (e.g., fistulas, strictures) already at diagnosis [4,11].

At diagnosis, the heterogeneity in clinical presentation and subsequent disease course make clinicians' attempts to stratify the treatment according to the individual patient's needs very difficult. While some patients experience an indolent disease course with minimal symptoms and low endoscopic activity, a substantial proportion exhibit an aggressive disease phenotype

characterised by treatment refractoriness, corticosteroid dependency, frequent hospital admissions and surgical interventions, including resection surgery and acute colectomy [12–18]. For this latter group, an early effective treatment seems advantageous, as the initial disease phase may provide a "window of opportunity" where prompt suppression of intestinal inflammation could improve long-term outcomes [19–21]. Identifying prognostic biomarkers for this group of patients is therefore critical to facilitate the timely initiation of potent treatment.

To address the need for both diagnostic and prognostic biomarkers, we established the "Swedish Inception Cohort in IBD" (SIC-IBD), a large prospective multicentre cohort involving patients with suspected IBD referred to eight hospitals in Sweden. After a comprehensive diagnostic work-up, patients were classified as incident IBD patients or symptomatic non-IBD controls, i.e., patients presenting with symptoms mimicking IBD but where IBD was ruled out. Alternative diagnoses in this patient group included infectious colitis, irritable bowel syndrome and diverticulitis. As a second control group, healthy controls without gastrointestinal symptoms were recruited. This cohort provides a rich collection of biospecimens together with detailed phenotypic characterisation collected both at diagnosis and during follow-up. Herein, we present the study design and baseline characteristics of the participants in the SIC-IBD.

COHORT DESCRIPTION

Inclusion

This longitudinal multicentre cohort study was conducted across eight Swedish hospitals: Ersta Hospital, Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Södra Älvsborg Hospital, Uppsala University Hospital, and Örebro University Hospital. Patients aged ≥ 18 years with gastrointestinal

symptoms, such as diarrhoea, abdominal pain and blood or mucus in stools, who were referred to the gastroenterology unit with suspected IBD between November 2011 and March 2021 were eligible for inclusion (Figure 1). Exclusion criteria included a previous diagnosis of Crohn’s disease, ulcerative colitis or IBD unclassified, or inability to provide informed consent or to comply with protocol requirements. After obtaining written informed consent, all patients underwent a routine diagnostic work-up for IBD, following clinical practice and international guidelines [22].

Based on the diagnostic work-up, which included magnetic resonance imaging in cases where small bowel involvement was suspected, patients were classified as having incident IBD or as symptomatic controls, i.e., patients with no discernible evidence of IBD at inclusion or during follow-up. The diagnosis of IBD was based on internationally accepted clinical, endoscopic, radiological, and histological criteria [22]. Nine patients were excluded due to suspected or confirmed IBD during follow-up. Patients are followed prospectively according to clinical practice, with data collected after 3 months, 1, 3, 5, 7 and 10 years for those with IBD. At present, follow-up is ongoing for many patients. In addition, a group of healthy controls, without gastrointestinal disease, was included at baseline.

Demographics of patients and controls

During the inclusion period, 367 patients with IBD (Crohn’s disease, n=142; ulcerative colitis, n=201; IBD-U, n=24) and 168 symptomatic controls were included (Table 1). The group of symptomatic controls comprised patients who ultimately were diagnosed with various diseases, including microscopic colitis, infectious enteritis, celiac disease, or irritable bowel syndrome. In addition, 59 healthy controls without any history of gastrointestinal disease were recruited as a second control group.

Table 1. Demographics of individuals included in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24	Symptomatic control n=168	Healthy control n=59
Female sex, n (%)	72 (50.7)	81 (40.3)	11 (45.8)	107 (63.7)	33 (55.9)
Median age (IQR)	28 (23-41)	34 (26-45)	33 (30-45)	34 (25-48)	26 (23-31)
Median CRP, mg/L (IQR)*	8.0 (3.2-32.3)	3.7 (1.4-8.7)	3.1 (2-5.6)	1.8 (0.9-5.9)	0.6 (0.3-1.1)
Median FCP, µg/g (IQR)*	452 (234-981)	325 (90-880)	471 (148-621)	68 (19-146)	10 (5-24)
Smoking, n (%)					
Never	81 (57)	104 (52)	13 (54)	76 (45)	43 (73)
Previous	28 (20)	64 (32)	8 (33)	30 (18)	10 (17)
Current	25 (18)	16 (8)	2 (8)	18 (11)	4 (7)
Missing	8 (6)	17 (8)	1 (4)	44 (26)	2 (3)
Median BMI, kg/m ² (IQR)	23 (21-26)	24 (22-27)	27 (22-28)	26 (22-30)	23 (21-25)

*Information was missing for CRP in 62 (10%) individuals, faecal calprotectin in 217 (37%) individuals and for Body Mass Index in 197 (33%) individuals.
CRP: C-reactive protein; IQR; interquartile range; FCP, faecal calprotectin.

Healthcare setting

Sweden has a tax-funded universal healthcare system, and private outpatient healthcare providers are few within the field of gastroenterology. In general, gastroenterologists at secondary or tertiary care centres (rather than primary care) are responsible for diagnosing and managing patients with IBD.

Data collection

Characterisation of disease phenotype and disease activity

Following informed consent, data on patient demographics, disease phenotype according to the Montreal classification[23], extraintestinal manifestations, endoscopic activity (defined as the presence of ulcers in Crohn's disease [yes/no] and the Mayo endoscopic subscore in ulcerative colitis), IBD treatment, IBD-related surgery, and hospital admission were recorded at baseline and prospectively during follow-up. Treatment-naivety was defined as no prior treatment with IBD-related medications, including topical therapies. Previous treatments in patients who were not treatment-naïve included mostly topical therapies but also a few days of corticosteroid treatment. For healthy controls, information about basic demographics was collected. Data on disease characteristics were recorded using case report forms (CRFs), and details on the Montreal classification and clinical disease activity at baseline are provided in **Table 2**.

Table 2. Clinical characteristics of patients with Crohn's disease, ulcerative colitis and IBD-unclassified in the Swedish Inception Cohort in IBD (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD-unclassified n=24
Disease location, n (%)			
ileal (L1)	48 (34)		
colonic (L2)	50 (35)		
ileocolonic (L3)	34 (24)		
upper GI (L4)	1 (1)		
unknown	9 (6)		
Disease behaviour, n (%)			
non-stricturing, non-penetrating (B1)	115 (80)		
stricturing (B2)	14 (10)		
penetrating (B3)	5 (3)		
unknown	8 (6)		
Perianal disease, n (%)			
	12 (8)		
Disease extent, n (%)			
ulcerative proctitis (E1)		64 (32)	
left-sided colitis (E2)		57 (28)	
extensive colitis (E3)		76 (38)	
Unknown		4 (2)	
Treatment-naïve, n (%)			
	128 (90)	185 (92)	21 (88)

Upper GI (L4) refers to patients with only upper gastrointestinal Crohn's disease.

IBD-unclassified, Inflammatory bowel disease unclassified; SIC-IBD; GI, gastrointestinal.

Patient-reported outcomes

Patient questionnaires were employed to obtain information about clinical disease activity, smoking status, recent antibiotic or non-steroid anti-inflammatory drug use, and any specific dietary restrictions.

Patients were also asked to complete the Short-Health-Scale and Short Form-36 (SF-36) questionnaire to obtain information about Health-Related Quality of Life (HRQoL) [24–26]. SF-36 is a general measure of HRQoL, whereas the Short-Health Scale is a validated measure to address HRQoL in patients with IBD. It includes four dimensions: bowel symptoms, daily life activities, worry and general well-being. Additional quality of life data were collected using the EuroQol-5D (EQ-5D) questionnaire[27,28]. Mental health was evaluated using the Patient-health Questionnaire 9 (PHQ9) [29], the Cognitive Reserve Index (CRI) [30], and the Short-Form Health Survey (SF-36) [26]. Additional data on gastrointestinal symptoms was obtained by using the Gastrointestinal Symptom Rating Scale (GSRS) [31] and the Rome III criteria functional gastrointestinal disorders [32].

Sample collection and biobanking

Biospecimens were obtained at baseline and during follow-up, processed and biobanked according to predefined standard operating procedures (SOPs). Blood samples were collected in EDTA and PAX®-tubes. In addition, serum samples were obtained by centrifugation of whole blood at $2400 \times g$ for 5 min at ambient temperature, followed by aliquoting of serum and storing at $-80^{\circ} C$. For six centres, blood samples were shipped unprocessed at ambient room temperature and centrifuged upon arrival at the central biobank, Örebro, Sweden. The participants collected faecal samples in plastic tubes at home, brought them to the hospital or

mailed them by postal service. On arrival, the samples were immediately frozen and stored at -80°C. Spot urine samples were collected during study visits, aliquoted and stored at -80°C. In addition to collecting biopsies as part of clinical routine, physicians were instructed to take intestinal biopsies from both inflamed and non-inflamed mucosa according to a predefined protocol. These biopsies were preserved in Allprotect Tissue Reagent (Qiagen, Hilden, Germany) and in a bacterial freezing medium. Biopsies in the freezing medium were immediately stored at -80°C, whereas those in Allprotect Tissue Reagent were handled according to the manufacturer's instructions. Details on the collected biological material are provided in **Table 3**.

Table 3. An overview of biospecimens collected at baseline from individuals within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD)

	Crohn's Disease n=142	Ulcerative colitis n=201	IBD- unclassified n=24	Symptomatic control n=168	Healthy control n=59
Serum, n (%)	137 (96)	199 (99)	23 (96)	164 (98)	59 (100)
Faecal, n (%)*	99 (70)	137 (68)	20 (83)	112 (67)	56 (95)
Intestinal biopsies, n (%)	92 (65)	161 (80)	18 (75)	155 (92)	58 (98)
Urine, n (%)	62 (44)	91 (45)	9 (38)	90 (54)	58 (98)

*Faecal samples for microbiome analyses and for additional faecal marker. Samples for faecal calprotectin were handled separately.
IBD, inflammatory bowel disease.

Measurements of high-sensitivity CRP and faecal calprotectin

After storage, samples for high-sensitivity (hs) CRP (serum) and calprotectin (faeces) were retrieved from the central biobank and sent to Uppsala Clinical Research Center, Uppsala, Sweden and Academic Laboratory, Department of Clinical Chemistry, University Hospital,

Uppsala, Sweden, respectively. hsCRP was assayed in a single batch for all participants at the end of the recruitment period, using a particle-enhanced immunoturbidimetric hsCRP assay (Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics) on a Roche Cobas c501. Correspondingly, FCP was extracted and analysed according to the manufacturer's instructions, with a chemiluminescent immunoassay, using the LIASON XL analyser (DiaSorin, Saluggia, Italy). Data on median levels of hsCRP and FCP across the various diagnoses are provided in **Table 1**.

Disease course outcome during follow-up

A composite outcome measure was used to categorise the disease course as aggressive or indolent during follow-up. An aggressive disease course was defined as the presence of any IBD-related surgery, hospital admission for active disease, treatment refractoriness towards targeted therapies, i.e., biologics, Janus kinase (JAK) inhibitors or sphingosine-1-phosphate receptor modulators, and >two courses or high cumulative dosis of systemic corticosteroids within the first year of follow-up (**Table 4**). In addition, Crohn's disease patients with evidence of progression to a complicated disease behaviour, i.e., a new stricture, fistula, or abscess, were also categorised as having an aggressive disease course.

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Table 4. Criteria for defining the disease course as aggressive or indolent within the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD). Patients with any of the following events during the first year from the date of diagnosis were defined as having an aggressive disease course.

Difficulty in controlling inflammation in patients with IBD

- Hospital admission for active disease
- Surgical resection (including colectomy) or a stoma
- Use of > 2 courses of corticosteroids* or a cumulative dose of > 2.5 g equivalents of prednisolone
- Use of ≥ 2 targeted therapies due to poor clinical effectiveness**

Progression to complicated disease behaviour in patients with Crohn's disease

- New fistula (recto-vaginal, enterocutaneous, internal or proctitis-related perianal fistula), or need for fistula-related surgery
- New abscess (including perianal abscess) or abscess-related surgery
- New stricture or stricture-related surgery

*A corticosteroid course was defined as an episode of treatment with specified start and stop dates. Typically, oral prednisolone was initiated at a starting dose of 40 mg once daily, with a tapering schedule of 5mg per day at weekly intervals, resulting in an 8-week treatment course. For oral budesonide courses, a fixed dose of 9 mg once daily for 8 weeks was most commonly applied.

**Targeted therapies were defined as biologics, Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators.

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Data management

Patients, physicians, or research nurses used CRFs and predefined questionnaires to collect information. All data were imported after pseudonymisation into a central database with reading access for all co-investigators. The database is updated every 6-12 months to allow the import of new data, including follow-up visits, address possible missing information, and correct potential erroneous data entries. To enable backward traceability, a data freeze is created at each update. Each data freeze provides a snapshot of information contained in the database at a given date.

Project organisation

The SIC-IBD represents a crucial element of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in IBD (BIO IBD), which aims to bring leading clinicians, clinical researchers and basic scientists within the field of IBD together with corporate partners. The managerial structure and the operational organisation of BIO IBD are shown in **Figure 2**. An executive office has been set up at the Faculty of Health and Medical Sciences, Örebro University, forming the BIO IBD Executive Committee together with representatives of participating universities and university hospitals. The Executive Committee coordinated the efforts of the work packages, clinical departments, biomedical companies, and the Swedish patients' organisation, *Mag- och tarmförbundet* [33].

The Steering Committee, responsible for the strategic leadership, is formed by representatives from involved universities, biomedical companies and the patient organisation, with equal numbers of basic scientists and clinicians, equal gender, and representation of young scientists. The Advisory Board, composed of internationally renowned representatives of academia and the biomedical industry, provides external review and input.

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295 Patient and public involvement

296 During the planning phase of the cohort study, patient representatives from the Swedish
297 patient's organisation, *Mag- och tarmförbundet* provided input on the study design, including
298 the definition of the disease course during follow-up. Also, they assessed the burden of the
299 collection of biological material and the time required for responding to the questionnaires in
300 the study. Representatives of the patient organisation and the Swedish biomarker manufacturers
301 in the executive committee also provided feedback during the recruitment process and follow-
302 up of study participants. In addition to scientific reporting, key findings of the studies will be
303 communicated to patient organisations, public health policymakers, and the public through
304 various media and news activities. When disseminating the results, the recommendations of the
305 International Committee of Medical Journal Editors (ICMJE) will be applied [34].

307 FINDINGS TO DATE

308 At baseline, differences in smoking habits were observed between patients with Crohn's disease
309 and ulcerative colitis. Active smoking was more prevalent in patients with Crohn's disease,
310 while a higher rate of former smokers was found in patients with ulcerative colitis. While
311 hsCRP measurements were available for 90% of all patients and controls, only 63% of patients
312 and controls had available FCP measures in the study. An additional 44 measurements of FCP
313 at diagnosis were available from clinical routine, but these results were excluded from this
314 analysis due to the use of different assays. Both FCP and hsCRP levels were higher in patients
315 with Crohn's disease and ulcerative colitis compared to symptomatic controls and healthy
316 controls. However, while FCP levels were significantly elevated in IBD unclassified compared
317 to symptomatic controls, the difference in hsCRP levels between these two groups was not
318 statistically significant. No significant differences in FCP levels were observed between
319 patients with Crohn's disease and ulcerative colitis, but hsCRP levels were higher in Crohn's

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disease patients. Significant differences in hsCRP and FCP levels were also found between symptomatic controls and healthy controls.

Preliminary results from analyses of serum proteins as well as findings from the analyses of faecal markers have highlighted the potential of these markers to differentiate between patients with IBD and symptomatic controls in this cohort, suggesting their diagnostic value [35,36]. Recent results from the analysis of anti- $\alpha\text{v}\beta 6$ autoantibodies further suggested a high diagnostic value for ulcerative colitis of this marker [37]. Additionally, preliminary data indicate differences in mucosal proteins between patients developing an aggressive course of ulcerative colitis and those with an indolent course [38].

In line with previous studies [19,39], we employed a composite outcome to characterise the disease course within the first year after diagnosis, either as aggressive or indolent (Table 4). An aggressive course was defined by treatment refractoriness, the need for surgical resection, or in the case of Crohn’s disease, the development of severe complications such as strictures and fistulas. Based on this definition, 37% (53/142) of the patients with Crohn's disease, 24% (48/201) of those with ulcerative colitis, and 4% (1/24) with IBD-U experienced an aggressive disease course within the first year after diagnosis (**Supplementary Table 1**). These results underscore that treatment failure rates and disease complications remain unacceptably high in IBD. Aggressive disease course was associated with more extensive ulcerative colitis, while no association was found between Crohn’s disease location and disease course.

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343 **Future plans**

344 Research projects and collaborations based on the SIC-IBD are ongoing. The diagnostic and
345 prognostic value of multiple molecular datasets is being further investigated, both separately
346 and in combination, using a multi-omics approach. Additionally, correlations across data layers,
347 such as between levels of faecal marker, serum and mucosal proteins, and compositional
348 microbiome data may provide further insights into disease mechanisms. The evaluation of the
349 patient-reported outcomes aims to improve our understanding of the impact of IBD on patients'
350 quality of life, and can be integrated with clinical and molecular data to explore potential
351 associations.

352
353 If single biomarkers or biomarker signatures of markers are identified, we aim to validate these
354 in independent cohorts. For example, preliminary findings on serum proteins and results on
355 anti- $\alpha\text{v}\beta 6$ autoantibodies have been validated in the Inflammatory bowel disease in South-
356 Eastern Norway III (IBSEN III) cohort [35,37,40]. Conversely, SIC-IBD may also serve as a
357 validation cohort for findings from other cohorts. For instance, recent results on serum proteins
358 in preclinical IBD were examined in SIC-IBD to evaluate their relevance in incident IBD [41].
359 Finally, promising markers from the SIC-IBD should be further tested in prospective clinical
360 trials, such as the NORDTREAT trial [42].

361 362 **STRENGTHS AND LIMITATIONS**

363 In this large nationwide multicentre inception cohort of newly diagnosed patients with IBD, a
364 set of highly relevant biospecimens were collected at inclusion, and patients were prospectively
365 followed. This cohort can be used to gain insights into key pathogenic mechanisms of IBD.
366 Moreover, it provides a valuable resource for biomarker discoveries, particularly the

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367 identification of diagnostic biomarkers for IBD and prognostic markers for future disease
368 courses.

369 This cohort is one of few large-scale IBD inception cohorts of adult patients with integrated
370 biobanking [40,43,44], as most of the earlier initiatives have included paediatric patients only.
371 Most previous attempts to identify diagnostic biomarkers in inception cohorts have used healthy
372 controls or patients with non-inflammatory conditions (e.g., irritable bowel syndrome) as a
373 control group. These settings do not reflect a diagnostic scenario where patients with
374 gastrointestinal symptoms that are indicative of IBD are examined. Accordingly, evaluations
375 based on these cohorts are likely to overestimate the diagnostic capacity of potential biomarkers
376 [45]. However, this limitation is rarely acknowledged and may partly explain why promising
377 biomarkers fail in replication attempts and do not make their way to the clinic. To allow the
378 identification of diagnostic biomarkers, we have included patients with symptoms indicative of
379 IBD but without any signs of the disease at diagnostic work-up or during follow-up
380 (symptomatic controls) as a reference group. Thus, both cases with IBD and symptomatic
381 controls represented an unselected sample of patients who were referred to secondary care for
382 the suspicion of IBD. In addition, we included healthy controls as a second control group to
383 gain insight into the aetiology of IBD and to characterise pathways related to disease
384 pathogenesis.

385 A composite outcome was chosen to categorise disease course since no established gold
386 standard for defining or classifying IBD course currently exists. The Montreal classification
387 provides a framework for Crohn’s disease location and behaviour, and extent of ulcerative
388 colitis but does not capture disease progression over time [23]. Several other cohorts, including
389 the European Crohn’s and Colitis Organization’s Epidemiological Committee (EpiCom)
390 inception cohort [14] and the IBSen III cohort [40], have recorded disease-related events such
391 as IBD-related surgery, disease complications, and hospital admissions to assess disease

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severity over time. Similarly, the Randomised Evaluation of an Algorithm for Crohn's Treatment (REACT) [19] and REACT-2 [39] trials employed a composite outcome to define disease course in Crohn's disease using similar criteria. While a single criterion, such as treatment escalation or new disease complications in Crohn's disease [46,47], may facilitate interpretability, a composite outcome allows a more comprehensive assessment of disease severity over time. This approach captures multiple dimensions, including difficulties in controlling inflammation, fibrosis-related complications, and poor treatment response, thereby offering a broader perspective on disease course.

In this cohort, we did not record the number of eligible patients who were not included, e.g. those who declined to or were not able to give informed consent or were not identified by study personnel. The absence of a population-based cohort design could be a limiting factor when interpreting associations between exposures and clinical outcomes within SIC-IBD, as selection bias may have been introduced. However, the proportion of IBD patients with Crohn's disease in this study (39%), the EpiCom inception cohort (37%) and the recent population-based IBSEN III cohort (35%) were similar. Likewise, the proportions of ulcerative colitis (55%, 52% and 61%) and IBD-U (7%, 11% and 4%) were similar in the three cohorts. Suboptimal procedures in sample collection further limited the study. To enable inclusion at all centres, serum samples collected at centres with limited sample processing capacity were shipped overnight to a central biobank for centrifugation and biobanking. While measured faecal markers such as calprotectin are stable at room temperature for several days, microbiome analyses are sensitive to pre-analytic sample handling [48–50]. Furthermore, not all included patients were treatment-naïve, which could influence the molecular data and may warrant sensitivity analyses. Approximately 9% of patients had initiated treatment before inclusion, most commonly with one or a few doses of corticosteroids in the days preceding inclusion.

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COLLABORATION

We have established an inception cohort of newly diagnosed adult patients with IBD, symptomatic controls and healthy controls with integrated biobanking. Initiatives are underway to generate various multi-omics data from samples collected at baseline and follow-up visits. Analyses of single and multiple datasets, including integration of clinical variables, may discover novel diagnostic and prognostic biosignatures for IBD and its subtypes. Comparisons with healthy controls may also provide insights into IBD pathogenesis and progression mechanisms. We encourage collaborations with researchers from other cohorts and case-control studies to validate findings from the SIC-IBD cohort. Also, researchers can propose new collaborative initiatives and apply for access to data and biospecimens by submitting a proposal to the BIO IBD Executive Office (BIO.IBD@oru.se). All proposals will be reviewed on scientific quality and methodology by the BIOIBD executive committee.

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Contributors

Conception and design: JH. Drafting the manuscript: BS, OGrännö and JH. Critical revision for intellectual content, final approval, and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved: BS, OGrännö, DB, HS, AC, HH, MLL, JPH, SA, FB, CE, OGrip, AB, JM, NN, SB, CML, EHH, MKM, ÅVK, MD'A, DR, LÖ, JDS, MC, CRHH, RK, and JH. Guarantor: JH.

Competing interests

DB served as a speaker and/or advisory board member for Abbvie, BMS, Johnson and Johnson, Pfizer, Pharmacosmos, Sandoz, Takeda and Tillotts Pharma. HS has served as speaker and/or advisory board member for AbbVie Ferring, Janssen, Pfizer, Takeda, Gilead and Tillotts Pharma. AC served as a speaker for Takeda and Ferring. HH has served as a speaker, consultant or advisory board member for AbbVie, Ferring, Fresenius Kabi, Janssen, Norgine, Pfizer, Pharmacosmos, Takeda and Tillotts and has received grant support from AbbVie, Ferring, Takeda, and Tillotts. SA served as a member for Scientific committee/Advisory board of, Janssen, Pharmacosmos, Takeda, as a consultant for Janssen, OrionPharm, Takeda, and as a speaker: Galapagos, Janssen, Tillotts, received research grants from Janssen and OrionPharma. FB has acted as national and/or local principal investigator for clinical trials for Janssen, Ferring and Abbvie. CE received grant support/lecture fee/advisory board from Takeda, Janssen Cilag, Pfizer, Abbvie. OGrip served as speaker and/or advisory board member for Abbvie, Bristol Mayer Squibb, Eli Lilly, Ferring, Janssen, Pfizer Takeda, Tillotts Pharma and Vifor Pharma. JM has served as a speaker, consultant or advisory board member for AbbVie, Alfasigma, Amgen, Bayer, Biogen, BMS, Eli Lilly, Ferring, Galapagos, Hospira, ITH, Janssen, Lument, MSD, Otsuka, Pfizer, Sandoz, Takeda, Tillotts and UCB; and has received grant support (not for this study) from AbbVie, BMS, Calpro AS, Carbiotix, Ferring, Fresenius Kabi, Pfizer, Svar

Life Science and Takeda. MKM has received speaker's fees from Takeda and Janssen. LÖ has received a financial support for research by Genetic Analysis AS, Biocodex, Danone Research and AstraZeneca and served as Consultant/Advisory Board member for Genetic Analysis AS, and as a speaker for Biocodex, Ferring Pharmaceuticals, Takeda, AbbVie, Novartis, Janssen-Cilag and Meda. MC has received speaker's fees from ViforPharma. She is the national PI for clinical trials for AstraZeneca. CRHH has served as a speaker and/or advisory board member for AstraZeneca, Dr Falk Pharma and the Falk Foundation, Galapagos, Janssen, Pfizer, Takeda, Tillotts Pharma, and received grant support from Tillotts and Takeda. JH served as speaker and/or advisory board member from AbbVie, Alfasigma, Aqilion, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma and the Falk Foundation, Eli Lilly, Ferring, Galapagos, Gilead, Hospira, Index Pharma, Janssen, MEDA, Medivir, Medtronic, Merck, MSD, Novartis, Pfizer, Prometheus Laboratories Inc., Sandoz, Shire, STADA, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB and received grant support from Janssen, MSD and Takeda. The remaining authors declare no conflicts of interest.

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Ethical approval

The SIC-IBD study was approved by the Regional Ethics Committees (Dnr 2010/313). Written informed consent was obtained from all participants before inclusion.

Provenance and peer review

Not commissioned; externally peer-reviewed.

490 Data availability statement

491 Researchers can apply for access to data and biological specimens by submitting a proposal to
492 the BIO IBD Executive Office (BIO.IBD@oru.se), including a copy of their ethics approval.
493 All proposals will be reviewed by the BIOIBD executive committee based on scientific quality
494 and methodology. This procedure is installed to ensure that the clinical data and biological
495 material are being requested for scientific purposes, in accordance with the informed consent
496 signed by the participants, as the collected data and material cannot be used by purely
497 commercial parties. Additionally, any transfer of data or biological material must comply with
498 Swedish law and the European Union (EU) General Data Protection Regulation (GDPR).
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FIGURE CAPTIONS

Figure 1. Flow diagram showing the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

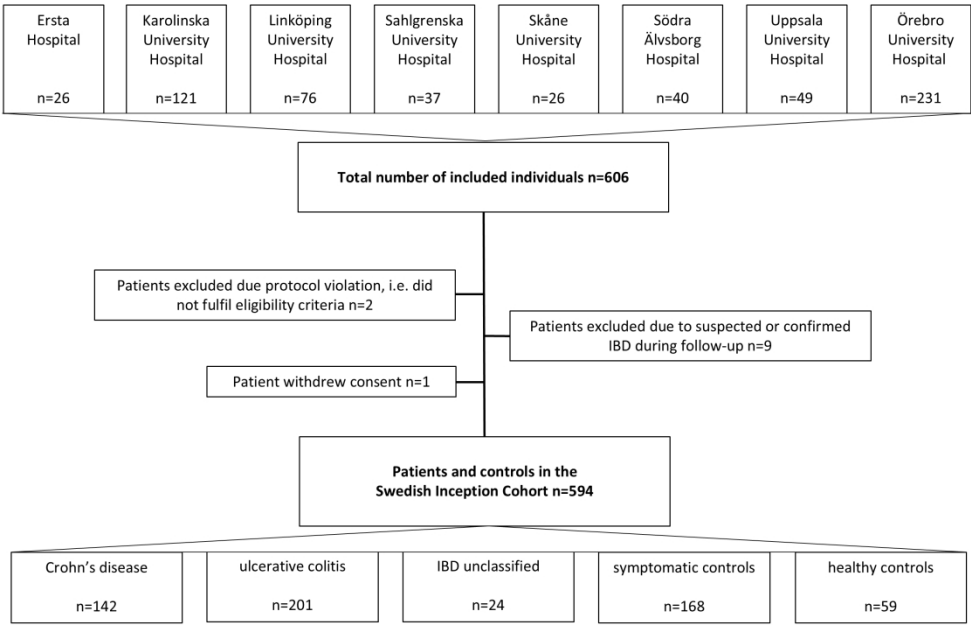


Figure 1. The flow diagram shows the number of included individuals at each hospital, the number of patients excluded and the final number of patients and controls in the Swedish Inception Cohort in inflammatory bowel disease (SIC-IBD).

609x395mm (118 x 118 DPI)

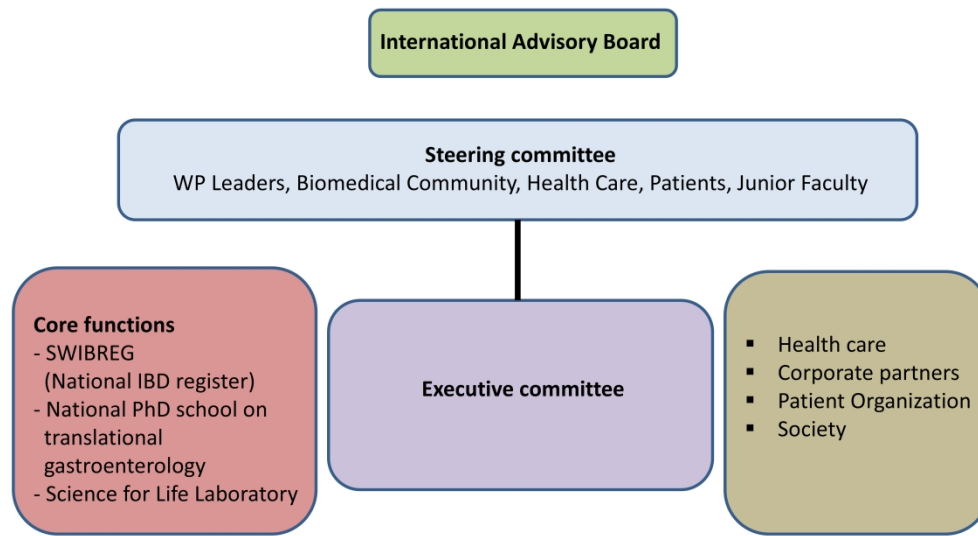


Figure 2. Managerial structure and the operational organisation of the multi-modal national study to identify biomarkers for diagnosis, therapy response and disease progression in inflammatory bowel disease (BIO IBD), where the Swedish inception cohort in IBD (SIC-IBD) represents an important resource.

611x334mm (236 x 236 DPI)

Supplementary Table 1

	Crohn's disease n=142	ulcerative colitis n=201	IBD-unclassified n=24
Aggressive disease, n (%)	53 (37.3)	48 (23.9)	1 (4.2)
Indolent disease, n (%)	83 (58.5)	144 (71.6)	22 (91.7)
Unknown*, n (%)	6 (4.2)	9 (4.5)	1 (4.2)

*Missing information about clinical outcomes due to incomplete follow-up during the first year after diagnosis.