

# BMJ Open Influence of Genetics, Immunity and the Microbiome on the Prognosis of Inflammatory Bowel Disease (IBD Prognosis Study): the protocol for a Copenhagen IBD Inception Cohort Study

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## ABSTRACT

**Introduction** Inflammatory bowel diseases (IBD), encompassing Crohn's disease and ulcerative colitis, are chronic, inflammatory diseases of the gastrointestinal tract. We have initiated a Danish population-based inception cohort study aiming to investigate the underlying mechanisms for the heterogeneous course of IBD, including need for, and response to, treatment.

**Methods and analysis** IBD Prognosis Study is a prospective, population-based inception cohort study of unselected, newly diagnosed adult, adolescent and paediatric patients with IBD within the uptake area of Hvidovre University Hospital and Herlev University Hospital, Denmark, which covers approximately 1 050 000 inhabitants (~20% of the Danish population). The diagnosis of IBD will be according to the Porto diagnostic criteria in paediatric and adolescent patients or the Copenhagen diagnostic criteria in adult patients. All patients will be followed prospectively with regular clinical examinations including ileocolonoscopies, MRI of the small intestine, validated patient-reported measures and objective examinations with intestinal ultrasound. In addition, intestinal biopsies from ileocolonoscopies, stool, rectal swabs, saliva samples, swabs of the oral cavity and blood samples will be collected systematically for the analysis of biomarkers, microbiome and genetic profiles. Environmental factors and quality of life will be assessed using questionnaires and, when available, automatic registration of purchase data. The occurrence and course of extraintestinal manifestations will be evaluated by rheumatologists, dermatologists and dentists, and assessed by MR cholangiopancreatography, MR of the

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study is a prospective population-based inception cohort study of all newly diagnosed patients with inflammatory bowel diseases patients, both adult, adolescent and paediatric, within a well-described geographical area, ensuring the cohort represents the whole spectrum of disease presentation and course.
- ⇒ The longitudinal study design, with regular collection of biological material, will enable investigations of the underlying mechanisms of the heterogeneous courses of IBD.
- ⇒ In this study population, the occurrence and course of some of the most common subclinical and clinical extraintestinal rheumatological, dermatological, oral and hepatobiliary manifestations will be thoroughly described.
- ⇒ Although well described, the cohort is limited by its sample size when compared with existing prospective population-based cohorts.
- ⇒ Due to the nature of the study design, missing data and biological samples are expected in some patients.

spine and sacroiliac joints, ultrasonography of peripheral joints and entheses, clinical oral examination, as well as panoramic radiograph of the jaws. Fibroscans and dual-energy X-ray absorptiometry scans will be performed to monitor occurrence and course of chronic liver diseases, osteopenia and osteoporosis.

**Ethics and dissemination** This study has been approved by Ethics Committee of the Capital Region of Denmark (approval number: H-20065831). Study results will be disseminated through publication in international scientific journals and presentation at (inter)national conferences.

## INTRODUCTION

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive, inflammatory diseases of the gastrointestinal (GI) tract. The pathogenesis of CD and UC is not fully understood but is thought to be the result of a complex interplay between genetic and environmental factors, epithelial barrier defects and altered gut microbiota, resulting in chronic relapsing innate and adaptive immune responses.<sup>1 2</sup> The incidence of IBD is increasing worldwide, and in Europe alone, more than 1.3 million people are affected.<sup>3</sup> Denmark has one of the highest prevalence in the world, with 0.8% of its population diagnosed with IBD.<sup>4</sup> The disease course of IBD is highly heterogeneous with some patients experiencing only mild inflammation and few symptoms, while others develop severe inflammation and complications.<sup>5 6</sup> Prospective population-based studies have recently demonstrated that a significant proportion of patients experience disease progression within the first 5 years of their diagnosis that requires hospitalisation, IBD-related surgery, and advanced therapy.<sup>5 6</sup> Patients diagnosed in childhood (20%), and specifically those with a very early onset of IBD, have more widespread disease, higher need for more aggressive treatment and have increased risk of cancer and mortality compared with patients diagnosed as adults.<sup>7</sup>

Furthermore, up to 50% of patients with IBD experience extraintestinal manifestations (EIMs) of IBD or immune-mediated inflammatory diseases (IMIDs) before or during the disease course of IBD.<sup>8-10</sup> Most commonly, EIMs occur in the musculoskeletal, dermatological, hepatopancreatobiliary and ocular organ systems.<sup>11-13</sup> Some EIMs, IMIDs (such as spondyloarthritis or psoriasis) and IBD share common inflammatory mechanisms<sup>14</sup> and environmental factors<sup>15</sup> that are associated with increased morbidity and mortality.<sup>16 17</sup> In addition, oral health status (ie, presence/absence of periodontitis, caries, periapical lesions) including the composition of the oral microbiome has been frequently discussed in the last decade as potentially relevant factor for IBD development, severity and progression.<sup>18-24</sup> Based on the results of a recent questionnaire-based, case-control study performed in Denmark a significant association between diagnosis and severity of IBD, periodontitis and tooth loss rate was confirmed.<sup>25 26</sup> Exploration of the pathogenesis of EIMs, including their overlap with IBD, might help clarify whether EIMs are systemic manifestations directly related to the intestinal disruptions of IBD, or whether these clinical conditions represent an abnormal, genetically mediated immunological response to complex environmental stimuli. Such efforts could facilitate the identification of

novel pathogenic pathways that can be targeted by individually tailored treatments.

Changes in the disease course of IBD are believed to be determined by factors within the first few years following diagnosis.<sup>27</sup> Therefore, it is important to identify patients at an early stage who might later develop aggressive disease to offer these patients closer follow-up and individually tailored therapy.<sup>28</sup> Currently, physicians rely on relatively poor predictors of the disease course of UC and CD when managing patients with these diseases. In UC, current predictors include young age at diagnosis and extensive disease, which have been shown to be associated with an increased risk of acute severe UC.<sup>29</sup> Accordingly, specific phenotypic appearances of CD, including perianal and upper GI involvement, have been shown to be predictive of disabling disease.<sup>30 31</sup> Second, environmental risk factors, such as smoking, are associated with increased risk of medical refractoriness in patients with CD.<sup>32</sup> Third, intestinal ultrasonography (IUS), a non-invasive modality for the assessment of disease activity and complications, has shown potential in predicting therapeutic response and risk of surgery.<sup>33-35</sup>

Gut microbiomes may fluctuate with IBD activity, and cytokine profiles in patients with IBD likewise seem to change over time.<sup>36 37</sup> Changes in these measures might therefore predict the disease course of IBD and the response to IBD medications.<sup>38</sup> Similarly, interactions between host and gut microbiota might play a role in IBD pathogenesis and thus warrant further research in representative cohorts.<sup>39</sup> For example, it has been very recently reported that the gut microbiome of patients with IBD—in contrast to the gut microbiome of IBD-free controls—is significantly more alike to the oral microbiome.<sup>40 41</sup> Recent preclinical trials investigating different mechanisms of the potential interplay between periodontitis and IBD have quite consistently shown the potential devastating effect of the oral microbiome on IBD pathogenesis and course, and a potentially positive effect of periodontal treatment on gut microbiome.<sup>41</sup> A prospective investigation of the changes over time in all biological and environmental exposure patterns is necessary to assess their interactions and associations with the disease course which might ultimately facilitate development and implementation of precision medicine in the care of patients with IBD.

## STUDY AIMS

IBD Prognosis Study aims to establish a prospective population-based cohort with an organised biobank system, from the time of diagnosis and added to throughout follow-up in order to characterise and predict the individual disease courses and treatment responses in patients with IBD. The primary and secondary aims are listed in [table 1](#).

**Table 1** Primary and secondary aims of the IBD Prognosis Study

Primary aims	To identify differences in microbial (mucosal and luminal), serological, environmental and genetic profiles (collectively called ‘biological profiles’) between phenotypes of patients with IBD of all ages at the time of diagnosis
	To determine associations between changes in the biological profiles and disease outcomes, including changes in phenotype, hospital admissions, surgeries and treatment responses
	To determine associations between biological profiles and disease activity and severity in terms of endoscopic severity, intestinal damage as determined by imaging assessment and objective markers of inflammation
	To identify novel biological markers that can predict the disease course of IBD
	To determine the distribution of inflammatory (and structural) lesions in axial and peripheral joints and entheses of patients with IBD
	To investigate and compare the musculoskeletal imaging findings with the musculoskeletal clinical examination and the imaging and clinical factors associated with IBD activity in musculoskeletal symptomatic and asymptomatic patients with IBD
Secondary aims	To describe the occurrence of IBD in a population-based cohort of both adult-onset and paediatric-onset patients
	To describe the natural history of IBD, including disease progression and prognosis
	To identify clinical markers associated with the prognosis and disease progression
	To investigate the impact of medical and surgical treatments of IBD on the disease course and prognosis of IBD
	To describe the occurrence, pattern of involvement, and natural history of IMIDs and EIMs in patients with IBD
	To identify food purchase patterns, and novel biological and clinical markers, that can predict the disease course of IBD
	To assess the ability of IUS to predict clinical and objective disease course
	To validate the IBUS-SAS against objective measures of inflammation
	To assess changes in the oral microbiome and microbial proteome over time and in dependence of the disease course of IBD

IBD, inflammatory bowel diseases; EIM, extra-intestinal manifestation; IMID, immune-mediated inflammatory disease; IUS, intestinal ultrasound; IBUS-SAS, International Bowel Ultrasound Segmental Activity Score

## METHODS

### Study design overview

The IBD Prognosis Study is a population-based inception cohort study of newly diagnosed paediatric, adolescent and adult patients with IBD according to current diagnostic criteria (ie, Porto diagnostic criteria<sup>42</sup> or Copenhagen diagnostic criteria<sup>43</sup> within the 2-year period between 1 May 2021 and 30 April 2023.<sup>42 43</sup> Patients will be followed prospectively with regular clinical examinations, imaging assessments and collection of biological samples, as described below. While the study aims to follow all patients for 20 years after their diagnosis of IBD, samples for the biobank will be collected during the first 5 years of follow-up. The study will be conducted at the Department of Gastroenterology and Hepatology, Herlev University Hospital and at the Gastrounit and Department of Paediatrics, Hvidovre University Hospital. The Department of Paediatrics, Hvidovre University Hospital covers the paediatric uptake area of both Hospitals. Together, these two hospitals cover an uptake area of approximately 1 050 000 inhabitants in the Copenhagen area (~20% of the total Danish population).<sup>44 45</sup> Based on the current

incidence of IBD in Denmark, a total of 550 adult patients and 100 adolescent or paediatric patients is expected to be diagnosed with IBD throughout the inclusion period.<sup>4</sup>

### Follow-up

Follow-up visits will be scheduled according to the study timelines presented in [tables 2 and 3](#). Additional follow-ups will take place at the treating physician’s discretion in case of significant disease events, which are defined as IBD-related hospitalisation or disease progression necessitating intensification of treatment. The follow-up period is 20 years from diagnosis until 30 April 2043. During years 6–20, patients will only be followed through their medical records.

### Data collection and management

[Tables 2 and 3](#) provide the timeline for adult and paediatric patients, respectively.

The study outcome definitions and measures are listed in [table 4](#). At each visit, all IBD-related clinical data will be prospectively collected, including patient demographics, disease activity, phenotypical disease presentation, results

**Table 2** Study timeline for adult patients with inflammatory bowel diseases

Time point	Time of diagnosis	During the first year after diagnosis	At 12 months of follow-up	During the second year after diagnosis	At 24 months of follow-up	During years 3–5 after diagnosis:	At 60 months of follow-up	Years 6–20
		Minimum every third month and at events	Minimum every 6 months and at events	Minimum every 6 months and at events	Minimum every 6 months and at events	Minimum annually and at events	Minimum annually and at events	Minimum annually and at events
Frequency of visit								
Screening for inclusion	X							
Participant information and written informed consent	X							
Collection of information from medical record including any medical adverse events	X	X	X	X	X	X	X	X
Detailed environmental questionnaire	X							
Collection of purchase data	X	X	X	X	X	X	X	X
Clinical disease activity score	X	X	X	X	X	X	X	X
Collection of faecal sample and rectal swab	X	X	X	X	X	X	X	X
Collection of blood sample	X	X	X	X	X	X	X	X
Collection of saliva sample	X	X	X	X	X	X	X	X
Collection of biopsies at endoscopy	X	(X)	X	(X)		(X)	(X)	(X)
MR cholangio-pancreatography	X						X	
MR enterography	X		X			(X)	X	
Rheumatological assessment	X	(X)					X	
MRI of spine and sacroiliac joints	X	(X)					(X)	
US of peripheral joints end entheses	X	(X)					(X)	
Dermatological assessment	(X)	(X)	(X)	(X)			(X)	
DXA scan	X						X	
IUS	X	(X)	X			X	X	
Fibroscan	At sign of liver disease		At sign of liver disease					
Dental assessment	X		X		X		X	
Panoramic radiograph	X						X	

Continued

**Table 2** Continued

Time point	Time of diagnosis	During the first year after diagnosis	At 12 months of follow-up	During the second year after diagnosis	At 24 months of follow-up	During years 3–5 after diagnosis	At 60 months of follow-up	Years 6–20
Collection of dental treatment needs	X	X	X	X	X	X	X	X

(X) indicates that the investigation will be performed if clinically relevant. MR enterography will be performed after 5 years in patients with CD. Fibroscan will be performed if a FIB4 calculation is greater than 1.45.  
 CD, Crohn's disease; DXA, dual-energy X-ray absorptiometry; IUS, intestinal ultrasound.

of blood and stool samples, current medical therapy, surgery, hospitalisation and occurrence of cancers.

In addition, all medical adverse reactions will be recorded prospectively. During each follow-up time point, patients are systematically asked about any medical adverse events which are categorised according to the medical dictionary of regulatory activities (MedDRA) 18.1 (or newer) terminology (table 1). Severity of adverse events, which will be graded based on clinical examination, and its implications for clinical management will be monitored as well.

Study data will be collected and managed using electronic case report forms (eCRFs) in the Research Electronic Data Capture system.<sup>46</sup>

#### Imaging assessments

MR enterography will be performed in all patients at the time of diagnosis as part of their diagnostic workup. Additionally, patients with CD or an unclassified type of IBD will undergo MR enterography 12 months after diagnosis, and CD patients will also undergo it 5 years from diagnosis (tables 2 and 3). Results and images from any scheduled or unscheduled endoscopic assessments will be recorded. The images will be scored as specified in table 4. Paediatric patients younger than 16 with CD will receive an X-ray examination of the left hand and wrist to investigate growth impairment at the time of diagnosis, and repeatedly if indicated by their disease phenotype (table 3).

#### Intestinal ultrasound

The infrastructure of the IBD Prognosis Study will be used to conduct substudies of the use of IUS in assessing disease burden and of its use as an early detector of disease progression. As such, IUS is planned at diagnosis, and again at 3, 6 (if F-calprotectin is higher than 250 µg/g), and 12 months of follow-up, and annually thereafter. In case of IBD-related surgery, IUS will be performed preoperatively and as part of the postoperative assessment 6–12 months after surgery. Sonographic disease activity will be assessed in terms of bowel wall thickness, colour Doppler signal, inflammatory fat (i-fat) and bowel wall stratification. The IBUS-SAS score, which integrates these four items, will be calculated as well.<sup>47</sup> Scans will be performed systematically of the entire bowel, including the sigmoid colon, descending colon, transverse colon, ascending colon, cecum, terminal ileum and the proximal small bowel. Image acquisition, grading of parameters and documentation will follow the recommendations by Novak *et al.*<sup>47</sup> Additional details for the IUS substudies are described in online supplemental file 1.

#### Patient-reported outcomes

As specified in table 5, validated patient-reported outcomes (PROs) of clinical disease activity, environmental factors, disability and health-related quality of life will be collected throughout the study.

**Table 3** Study timeline for paediatric and adolescent patients with inflammatory bowel diseases

Time point	Time of diagnosis	During years 1–2 after diagnosis: Follow-up minimum every third month and at events	At 12 months of follow-up	During years 3–5 year after diagnosis: Follow-up minimum every 6 months and at events	60 months of follow-up	Years 6–20 Follow-up minimum annually and at events
Screening for inclusion	X					
Participant information and written informed consent (repeated at age 18)	X					
Collection of information from medical record including any medical adverse events	X	X	X	X	X	X
Impact III questionnaire	X	X	X	X	X	
Detailed environmental questionnaire	X				X	
Clinical disease activity	X	X	X	X	X	
Collection of faecal samples	X	X	X	X	X	
Collection of blood sample	X	X	X	X	X	
Collection of biopsies at endoscopy	X	(X)	X	(X)	(X)	
Collection of saliva sample	X	X	X	X	X	
MR cholangio-pancreatography		(X)			(X)	
MR enterography	X		X		X	
Rheumatological assessment	X		(X)		X	
Dermatological assessment	(X)	(X)	(X)	(X)	(X)	
Left-hand radiograph for bone age	X		X			
DXA scan	X				X	
IUS	X	(X)	X		X	
Collection of dental treatment needs	X	X	X	X	X	X

(X) indicates that the investigation will be performed if clinically relevant. DXA, dual-energy X-ray absorptiometry; IUS, intestinal ultrasound.

### Extra-intestinal assessments

MR cholangiopancreatography (MRCP) will be performed at the time of diagnosis and after 5 years in all adult patients with IBD to assess the occurrence and phenotype of co-occurring hepatobiliary diseases associated with IBD. An MRCP will only be performed in paediatric patients older than 6 years with two consecutive abnormal (more than two times the reference value) plasma alanine aminotransferase or Gamma-glutamyl transferase measurements. The imaging protocols are presented in online supplemental file 3.

Adult patients recruited during the first year of study will be examined by experienced rheumatologists, including a systematic clinical evaluation, MR of the spine and sacroiliac joints, as well as ultrasonographic evaluation of peripheral joints and entheses at the time of diagnosis and repeated after 5 years. The patients will also have a systematic analysis for Human Leucocyte Antigen B27 (HLA-B27) positivity, and will be asked to answer several PROs relating to rheumatological EIMs (online supplemental file 2). In addition, The Toronto Axial Spondyloarthritis Questionnaire on IBD (TASQ-IBD),<sup>48</sup> which is a validated screening tool for extra-intestinal

musculoskeletal symptoms will, along with the first examination and newly occurring rheumatological symptoms after 1 year, determine whether a patient will be offered an additional assessment 1 year after the diagnosis of IBD.

All adult patients recruited during the second year of study will be examined by experienced dentists, including a systematic clinical evaluation at the time of diagnosis and again after 12, 24 and 60 months. In addition, patients will be asked general questions on dental visit patterns, treatment needs, oral hygiene habits and occurrence of oral lesions, as well as questions on oral health-related quality of life (OHIP-5). Questions previously recommended for self-reported surveillance of periodontitis will also be asked to calculate the Periodontal Screening Score.<sup>49</sup> Panoramic radiographs of the jaws will be recorded at baseline and after 5 years. The type and amount of dental treatment performed will be extracted annually from the Danish Health Insurance Registry (SSSY register).

All adolescent and paediatric patients included during the 2-year inclusion period will be offered an assessment by a paediatric rheumatologist including a systematic clinical evaluation and systematic ultrasonographic assessment of peripheral joints and entheses at the time

**Table 4** Study outcome measures and definitions

Study outcome measures	Disease activity in the adult population: Harvey-Bradshaw Index <sup>54</sup> (HBI) for CD and Simple Clinical Colitis Activity Index <sup>55</sup> (SCCAI) for UC and IBD-U	
	Disease activity in the paediatric population: abbreviated Paediatric CD Activity Index for CD <sup>56</sup> (abbPCDAI) and Paediatric UC Activity Index <sup>57</sup> for UC and IBD-U (PUCAI)	
	Endoscopic activity: Mayo Endoscopic Score <sup>58</sup> in UC and SES-CD <sup>59 60</sup> in CD patients All endoscopic assessments will be recorded prospectively.	
	Cross-sectional imaging activity/severity will be assessed using the Lemann Index, Magnetic Resonance Index of Activity (MaRIA), and Short MaRIA for MR. IBUS-SAS and Lemann Index will be used for IUS. <sup>47 61</sup> Transmural remission defined as bowel wall thickness less than 3 mm without colour Doppler signal <sup>62</sup> All IUS assessments will be recorded prospectively.	
	Impairment of growth in paediatric-onset IBD using the Paris classification <sup>63</sup>	
	Delayed puberty in paediatric-onset IBD	
	Distribution of imaging findings of EIMs in peripheral and axial joints and entheses, assessed by validated scores for inflammation and structural damage	
	Musculoskeletal symptoms and signs, assessed by clinical examination, PROs and imaging	
	Occurrence of dental disease (ie, periodontal diseases, caries, endodontic lesions) and tooth loss	
	Study outcome definitions	Abdominal surgery: IBD-related surgery including resection, colectomies, balloon dilatation, strictureplasty, stoma surgery and perianal surgery
Perianal surgery: any perianal procedure related to fistula or abscesses in the perianal area		
Clinical disease activity, defined as follows: <ul style="list-style-type: none"> <li>▶ Adult CD: HBI (scores ≤4: clinical remission; scores 5–7: mild disease; scores 8–16: moderate disease; scores &gt;16: severe disease)<sup>54 64</sup></li> <li>▶ Paediatric CD: abbPCDAI (scores 0–9: inactive disease; scores 10–15: mild disease; scores 16–25: moderate disease; scores &gt;25: severe disease)</li> <li>▶ Perianal disease in CD: Perianal Disease Activity Index (scores ≤4: clinical remission; scores &gt;4: active disease)<sup>65</sup></li> <li>▶ Adult UC: SCCAI (scores ≤2: clinical remission; scores 3–5: mild disease; scores 6–11: moderate disease; scores ≥12: severe disease)</li> <li>▶ Paediatric UC: PUCAI (scores 0–9: inactive disease; scores 10–34: mild disease; scores 35–64: moderate disease; scores 65–85: severe disease)</li> </ul>		
Endoscopic disease activity, defined as follows: <ul style="list-style-type: none"> <li>▶ CD: SES-CD (scores &lt;2: endoscopic remission; scores 3–6: mild endoscopic activity; scores 7–15: moderate endoscopic activity; scores &gt;15: severe endoscopic activity)<sup>59 60</sup></li> <li>▶ UC: Mayo Endoscopic Score (scores &gt;1: active disease)<sup>58</sup></li> </ul>		
Non-response/loss of response to medical treatment: either no change or an increase in disease activity following treatment initiation		
Malignancy: Any malignancies will be registered		
Mortality: All-cause mortality will be registered		
Biological treatment including time to this end-point and indicated hereof: Treatment of IBD or IMIDs with biological therapies, including antibodies against TNF- $\alpha$ , integrin $\alpha 4\beta 7$ , IL12/23, JAK inhibitors and future anti-IBD targets and small molecules		
In paediatric IBD: Growth impairment, as defined by the Paris classification <sup>63</sup>		
In paediatric IBD: Delayed onset of puberty defined as no breast development at age 13 in girls or a bilateral testis volume of less than 3 mL at age 14 in boys		
Occurrence of gingivitis or periodontitis according to the current classification system, <sup>66 67</sup> occurrence of caries, occurrence of endodontic lesions, and occurrence and reason for tooth loss, occurrence of peri-implantitis <sup>68</sup>		
CD, Crohn's disease; EIMs, extra-intestinal manifestations; IBD, inflammatory bowel disease; IMIDs, immune-mediated inflammatory diseases; IUS, intestinal ultrasonography; PROs, patient-reported outcomes; SES-CD, Simple Endoscopic Score for Crohn Disease; UC, ulcerative colitis.		

of the IBD diagnosis. Disease activity will be evaluated according to the Juvenile Arthritis Disease Score with the same frequency of examinations as adults.<sup>50</sup> In addition,

measurements of HLA-B27, antinuclear antibodies and rheumatoid factor will be performed in all adolescent and paediatric patients at the time of diagnosis of IBD.

**Table 5** Questionnaires and patient-reported outcomes

	Adult cohort	Paediatric cohort
Disease-specific	For Crohn's disease	
	HBI <sup>54</sup> PDAI <sup>65</sup>	AbbpCDAI <sup>56</sup> PDAI <sup>65</sup>
	For ulcerative colitis or unclassified IBD	
	SCCAI <sup>55</sup>	PUCAI <sup>57</sup>
Quality of life	EQ-5D <sup>69</sup> SIBDQ <sup>70</sup> IBD-DI <sup>71</sup> FACIT-F <sup>72</sup> OHIP-5	IMPACT III <sup>73</sup>
Evaluation of musculoskeletal and dermatological symptoms	Section 3.3.4 and online supplemental file 2	JADAS <sup>50</sup>
Environmental factors	Revised version of environmental factors scheme by IOIBD <sup>74</sup> Dietary questionnaire ('Hjertekost') <sup>75</sup>	Revised version of environmental factors scheme by IOIBD <sup>74</sup> Dietary questionnaire ('Hjertekost') <sup>75</sup>
AbbpCDAI, Abbreviated Paediatric CD Activity Index; EQ-5D, European Quality of life - 5 Dimensions; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HBI, Harvey-Bradshaw Index; IBD-DI, Inflammatory Bowel Disease-Disability Index; IOIBD, International Organisation of Inflammatory Bowel Disease; JADAS, Juvenile Disease Activity Score; PDAI, Perianal Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index; SCCAI, Simple Clinical Colitis Activity Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.		

However, in contrast to adult patients, adolescent and paediatric patients will only receive an MR scan of the spine and sacroiliac joints at the diagnosis of IBD if it is considered clinically relevant.

Adolescent and paediatric patients recruited during the second year of study will not be examined by dentist; however, dental radiographs will be requested annually from the national paediatric dental system ('Skoletandpleie'). Additionally, the number and type of periodontal treatments, fillings and endodontic treatments will be collected annually via the Danish Health Insurance Registry (SSSY register).

All patients who present dermatological manifestations will have these abnormalities photodocumented and evaluated by a dermatologist. If determined to be clinically relevant, the patient will be invited to a physical examination by a dermatologist, who will focus on IBD-associated EIMs and IMIDs, for example, hidradenitis suppurativa, pyoderma gangrenosum, erythema nodosum and psoriasis, which will be recorded in detail. Furthermore, all patients will undergo a regular screening by questionnaires for abscesses that could indicate hidradenitis suppurativa.<sup>51</sup> In such cases, an experienced hospital dermatologist will make an assessment and any instances

of hidradenitis suppurativa will be scored according to the recommended scoring indices (online supplemental file 2). When considering dermatological adverse events with difficulty in distinguishing these from new-onset distinct dermatological diseases, we will refer these patients to dermatologists as described above.

Finally, all adult, adolescent and paediatric patients are offered examination with a dual-energy X-ray scan at the time of diagnosis and after 5 years of follow-up to explore the occurrence and course of osteopenia and osteoporosis. Fibroscans are performed whenever patients present biochemical and clinical signs of chronic liver diseases.

#### Food purchase data

Adult patients are invited to participate in a substudy focusing on consumer data. Purchase data are to be automatically logged and collected throughout the study period using a mobile app, Storebox, which records all payment receipts made with credit cards, from participants using the digital receipt provider Storebox.<sup>52</sup> The aim of the substudy is to assess the purchase behaviour and its association and interplay with the disease course of IBD. Currently, more than one million Danes use the digital receipts provider, which covers three out of the six largest supermarket chains in Denmark. This method allows for in-depth and large-scale description of food-intake pattern over time, without the need for participants to invest their time in the sub study actively. Unfortunately, this method cannot distinguish food bought for the patients from those bought for offspring or partners.

#### Biological samples

Biological samples, including blood samples, rectal swabs, stool samples, saliva samples and swabs of the oral cavity, will be collected at the time of diagnosis and prospectively during each scheduled and unscheduled follow-up visit, as well as at the time of disease events in all participants. The biobanking of blood samples includes plasma, serum, buffy coat, PAXgene samples and whole blood samples.

At the time of diagnosis, four intestinal tissue biopsies (two snap-frozen and two held in RNA later) or two intestinal tissue biopsies (one snap-frozen and one held in RNA later) will be collected from five predefined intestinal segments, according to presence or absence of macroscopic inflammation, respectively. The five segments include the terminal ileum, cecum, transverse colon, sigmoid colon and rectum. Following diagnosis, two samples (one snap-frozen and one held in RNA later) will be collected from each segment and will be handled as described in table 6. Additional biopsies will be collected from other segments in the presence of inflammation.

#### Patient and public involvement statement

No patients were involved in formulating the research question or the outcome measures, nor in planning the study design.



**Table 6** Biobank of the IBD prognosis study

Biological sample	Medium/vial	Processing	Aliquoting	Storage	No of samples		
					Diagnosis	Regular follow-up	Events
Blood	9mL EDTA tube	Centrifugation at 3500rpm at room temperature for 10min	3 x EDTA plasma for protein analysis 1 x buffy coat for DNA analysis	−80°C	2x	1x	2x
	9mL serum tube	Sedimentation at room temperature for 30 min. Thereafter, centrifugation at 3500rpm at room temperature for 10 min	4 x serum for protein analysis	−80°C	2x	1x	1x
	2.5 mL PAX-gene RNA blood tube	21°C: 2 hour → −20°C: 24 hours → −80°C	1 x blood for RNA analysis	−80°C	2x	1x	1x
	4mL EDTA tube	Direct storage	Whole blood storage	−80°C	2x		
Swab	Faecal swab	Direct storage	1 x faecal sample for DNA analysis	−80°C	2x	1x	1x
Stool	Faecal tube with 96% ethanol	Direct storage	4 x faecal sample for DNA analysis	−80°C	2x	2x	2x
Intestinal biopsy	RNAlater stabilisation solution	Storage at room temperature for 24 hours	1 x biopsy for RNA analysis	−80°C	2x per segment	1 x per segment	1 x per segment
	Liquid nitrogen	Direct storage	1 x biopsy for backup	−80°C	2x per segment	1 x per segment	1 x per segment
Oral cavity	Unstimulated saliva sample	Direct storage (dry ice and in transport medium)	1x	−80°C	1x	1x	1x
	Swab	Direct storage (dry ice and in transport medium)	2x	−80°C	2x	2x	2x

IBD, inflammatory bowel diseases.

### Analysis plan for biological samples

#### Microbiota analysis and microbiota DNA sequencing

Stool and saliva samples will be analysed for microbiota, which will undergo 16S and 18S PCR (examining bacteria, fungi and parasites), Illumina sequencing and annotation of DNA sequences to the species level. These data will be analysed with in-house R-scripts or equivalent current standard platforms that will identify both quantitative and qualitative differences in microbiota between specific groups of patients.

#### Human metagenomic analysis

After removing the human sequences from the computer set by aligning the reads against the human reference genome, the remainder will then be compared with databases containing reads from previously identified pathogens and our own WGS database using the software MGmapper (<https://cge.cbs.dtu.dk/services/>

MGmapper/) or the equivalent current standard analysis platforms. To confirm that the microorganisms we find can be identified in the metagenomics analyses, we will perform single-nucleotide polymorphism analysis of the corresponding sequences found in the microbiome.<sup>53</sup>

#### RNA and protein extraction and analysis in both adult and paediatric populations

Buffy coat, intestinal biopsies and saliva samples will be analysed using a multiomics approach. RNA will be extracted from the standard punch biopsies of the intestine collected in RNAlater. Biopsies will then be transferred to a lysis buffer, homogenised and total RNA extracted simultaneously with protein and DNA fractions.

Global gene expression is to be analysed by RNA sequencing (Illumina PE150 system, Illumina, San Diego, California, USA) or the available platform at the time of analysis. Furthermore, gene analysis will focus on genes

related to IBD pathogenesis, EIM pathogenesis and pharmacodynamics and kinetics of IBD-related medicine. PCR analysis, Western blotting and immunohistochemistry will subsequently be used on the same subgroup of patients to confirm expression patterns of interest.

Live peripheral blood mononuclear cells derived from buffy coat from blood samples will be archived in a subset of the patients and handled in order to perform single-cell characterisation, including single-cell sequencing and multiparameter cytometry, to characterise the composition and activation status of innate and adaptive cell populations.

For the assessment of proteome profiles, the isolated protein fraction will be investigated with antibody-based multiplex analyses detecting proteins related to inflammation, barrier function, tissue degeneration, regeneration and fibrosis.

Blood samples will be centrifuged to obtain plasma and stored at  $-80^{\circ}\text{C}$  until needed for characterisation of preselected plasma proteins using inflammation assays.

Finally, metabolomics will be applied for the analysis of gut microbial metabolism as well as metabolic changes in patients with IBD using proton nuclear MR ( $^1\text{H-NMR}$ ) spectroscopy or mass spectrometry (MS).

### Statistical analysis

Statistics will be computed using IBM SPSS software V.28.0.1 or R V.4.1.0 or newer. Descriptive analysis of the baseline characteristics of the overall population and by gender will be conducted. Continuous variables will be presented as mean $\pm$ SD or median with IQRs and counting data will be presented as number and percentage (n, %). Comparison of groups will be conducted using t-test or Wilcoxon rank-sum test based on the type of distribution of data and homogeneity of variance.  $\chi^2$  test or Fisher's exact probability method will be used for counting data as appropriate.

The incidence rate of UC and CD and their disease events, as previously defined, will be estimated as the number of new cases of UC/CD or events divided by the total person-time at risk. The person-time at risk for each individual will be estimated as the time each participant remains free of events during the 20 years follow-up period. Survival analysis will be conducted using Kaplan-Meier curves and Cox proportional hazards method to calculate HRs with 95% CIs. In addition, multiple linear and logistical regression analysis will be used to evaluate the association between outcomes and potential risk factors. All models will be adjusted for potential confounding factors. In these regression analyses, missing data will be handled by the multiple imputation method. Participants lost to follow-up will be treated as right-censored data. A two-sided significance level of 0.05 will be used for all primary and secondary analyses unless stated otherwise.

Comparison of adult and paediatric data is not preprotocolled but might be conducted based on the findings.

### ETHICS AND DISSEMINATION

The protocol has been approved by the Ethics Committee of the Capital Region of Denmark (H-20065831) and the Danish Data Protection Agency (P-2020-1065). The study will be conducted in accordance with the ethical principles outlined in the current version of the Declaration of Helsinki and all applicable local regulatory requirements. Study results will be published according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

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