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ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

Specific phenotypes may drive an increased incidence of pediatric inflammatory bowel disease in South-Eastern Norway

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Abstract

Objectives: Pediatric inflammatory bowel disease (PIBD) incidence has increased in recent decades but may be stabilizing, prompting exploration of incidence changes, disease distribution, and severity.

Methods: From 2017 to 2019, patients under 18 years with PIBD symptoms were recruited from nine hospitals in South-Eastern Norway for Inflammatory Bowel Disease in South-Eastern Norway III (IBSEN III), a population-based inception cohort study. The primary outcome was a diagnosis of any PIBD subtype as defined by revised Porto criteria. Paris classification system defined disease phenotypes, and descriptions of covariates were gathered from patients in IBSEN III.

Results: We identified 324 PIBD patients, with 216 consenting to the IBSEN III study. The crude incidence rate was 17.8 per 100,000 person-years (PY) (95% confidence interval [CI]: 15.9–19.8). Crohn's disease (CD) was found in 118 patients (54.6%); 48% had ileocolonic distribution, 40% had upper gastrointestinal disease, and 12.8% had perianal disease. Complications (stricturing and/or penetrating) were noted in 18%. Ulcerative colitis (UC) was diagnosed in 78 patients (36.1%), predominantly pancolitis (41%), with 30% having proctitis. One in five suffered severe disease. IBD unclassified was found in 20 patients (9.3%). PIBD incidence in those under 16 was 13.6/100,000 PY, up from 4.7 in the IBSEN study 27 years ago. Terminal ileitis (11%–23%) and proctitis (14%–25%) rose from IBSEN (1990–1993) to IBSEN III, while stricturing/penetrating disease changed insignificantly (17%–16%).

Conclusions: The incidence of PIBD has risen in South-Eastern Norway, with increased cases of terminal ileitis in CD, unchanged stricturing/penetrating disease, and increased proctitis in UC compared to the original IBSEN study.

Trial registration: ClinicalTrials.gov identifier: NCT02727959.

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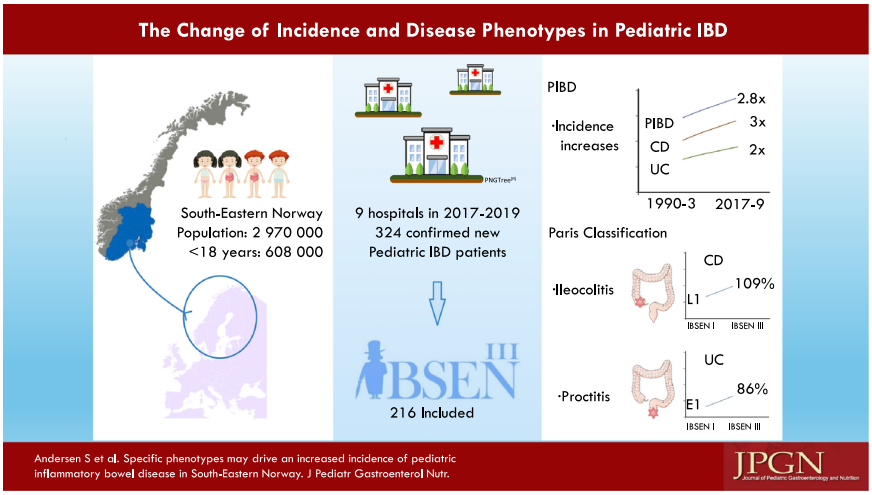

KEYWORDS
IBSEN III, Paris classification, PCDAI, population-based, PUCAI

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing, progressive disease that includes ulcerative colitis (UC), Crohn's disease (CD), and IBD-unclassified (IBDU). IBD is thought to be initiated by environmental triggers in genetically susceptible individuals that stimulate dysregulated inflammatory responses and alterations in the gut microbiome.[1] According to recent regional studies, 7%–12% of all new patients diagnosed with IBD are under 18 years old and have a more extensive disease compared to adult-onset disease.[2–4] Currently, there is no cure for IBD, and most pediatric patients require lifelong follow-up and treatment.[5,6] Its incidence increases rapidly in low- and middle-income countries and is highest in high-income countries.[7,8] The incidence of pediatric IBD (PIBD) in Nordic countries is among the highest reported worldwide. However, differences in phenotypic distribution between these countries have been demonstrated.[4,9–11] Furthermore, some data have suggested that the incidence rate may have reached a plateau in Nordic countries.[8] There is a lack of prospective population-based studies on large-scale, unselected, and treatment-naïve cohorts using standardized definitions, methodologies, and timescales with detailed information on the disease phenotypes and risk factors involved.[12,13] Knowledge about incidence development, disease distribution, and disease behavior in children needs to be updated.

This study aimed to (i) determine the incidence and (ii) clinical characteristics of PIBD at the time of diagnosis in South-Eastern Norway and compare our findings with those of previous studies in the same geographical area.

What is Known?

- The incidence of pediatric inflammatory bowel disease (PIBD) in Northern Europe is among the highest worldwide.
- The incidence of PIBD may have reached a plateau.

What is New?

- The incidence of PIBD in South-Eastern Norway has nearly tripled over the last 27 years, rising from 4.7 to 13.6 per 100,000 individuals under 16 years of age.
- The increase in the incidence of PIBD seems to be driven by specific, "adult-like" phenotypes, such as ileal inflammation in Crohn's disease (CD) and proctitis in ulcerative colitis; however, the complication rate of CD appears unchanged.
- Future research on etiology may concentrate on potentially skewed phenotype development and employ standard scales for symptom severity.

2 | METHODS

2.1 | Ethics statement

The Regional Committee for Medical and Health Research Ethics, South East Norway, and the Oslo University Hospital Data Protection Officer approved

this study (Ref: 2015/946-3). The IBSEN III study was registered in the Clinical Trials gov. no. NCT02727959. Written patient consent has been received and archived for all patients. The patients and their parents are informed of the intent to publish and have agreed to it. Patient representatives were included in the study, from planning to publication.

2.2 | Design and study population

The Inflammatory Bowel Disease in South-Eastern Norway III (IBSEN III) study is a population-based inception cohort study with prospective follow-up of children and adults. The South-Eastern health region has a total population of 2.95 million residents (56% of the Norwegian population).[14] Age-specific population estimates were obtained from Statistics Norway (SSB), based on the national registry (NR), which registers all residents in Norway with high documented accuracy.[15] The administration and organization of the IBSEN III study have been described elsewhere.[2]

2.3 | Inclusion and data collection

Patients under 18 years of age with suspected PIBD who were referred to local pediatric departments from 2017 to 2019 were invited to participate in the IBSEN III study based on their symptoms and medical history. All nine pediatric departments within the South-Eastern Health Region participated as study centers. After a comprehensive standardized workup, including clinical interviews, endoscopy, histology, biochemistry, and radiology, a pediatric gastroenterologist set the diagnosis and later reviewed it with another external pediatric gastroenterologist.

Patients with symptoms and findings that met the revised Porto criteria for PIBD were diagnosed as PIBD cases and included in the calculation of the crude incidence rate for the region.[16] (See flowchart in Figure S1.) PIBD cases with written informed consent were included in the IBSEN III study, and the inclusion date was defined as the date of diagnostic endoscopy. Patients exhibiting symptoms of PIBD but with normal work-up results were classified as "symptomatic controls." Patients with infections or other autoimmune or allergic explanations of their symptoms were excluded (Table S1). Diagnoses from cases that did not consent were registered anonymously and reported from each participating center as aggregated data. Anamnestic data, such as a family history of IBD, extraintestinal manifestations (EIMs), antibiotic use, or previous operations, were gathered directly from the clinical interview following the study protocol. Other information, including breastfeeding, birth method, and smoking habits, was obtained from electronic self-report forms. Early-onset IBD (EOIBD) was defined as PIBD occurring before the age of 10, while very early onset IBD (VEOIBD) was classified as occurring before the age of 6.

PIBD phenotypes were defined based on disease localization, extension, and behavior according to the Paris modified Montreal classification system.[17,18] The Mayo endoscopic score for UC and the modified simple endoscopic score for Crohn's disease (SES-CD) were used for endoscopic assessment.[19–21] Disease activity was evaluated using pediatric ulcerative colitis activity index (PUCAI) and pediatric Crohn's disease activity index (PCDAI) scoring systems.[22,23] To address potential selection bias, we assessed the effect of missing information on incidence rates and phenotypes between patients not included and those included in IBSEN III. Data from earlier IBSEN studies were gathered from the published data in addition to selected supplementary information from IBSEN I. All IBSEN III study-specific data were entered into an electronic clinical research form (eCRF) system (VieDoc®, PCG Solutions AB). The database was stored in services for sensitive data (TSD), designed and operated by the University of Oslo to store and postprocess sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Research Act." The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology framework for reporting standards in observational studies.

2.4 | Statistical analyses

Incidence figures were calculated using the number of PIBD diagnoses as numerators and the pediatric population in the South-Eastern Health region as denominators. The calculated annual incidence rates were based on the region's population numbers for 2017, 2018, and 2019 divided by age, and expressed per 100,000 person-years (PY). The population numbers for children younger than 1 year were divided by two when calculating PY, as birthdays were spread throughout the year. The estimated incidence rates were expected to be lower than 5% and assumed to be approximately normally distributed as a prerequisite for calculating the 95% confidence intervals (CIs).

Continuous variables were presented as median/interquartile range or mean/standard deviation, as indicated in the text, and categorical variables were presented as counts and proportions. To explore the possible relationships between PIBD and categorical variables, we used the chi-squared test or, for smaller samples, the Fischer exact test.

Continuous variables were compared using Student's *t*-test, Wilcoxon rank-sum test, or Kruskal–Wallis test, depending on the distribution and number of group

variables. Binary logistic regression was used to assess the impact of various covariates on the estimated risk of growth impairment. Statistical significance was set at $p < 0.05$. Data were analyzed using Stata software (v18 for Mac, StataCorp LLC).

3 | RESULTS

In total, 324 patients from all six pediatric departments in the region were diagnosed with PIBD between January 2017 and December 2019, out of a pediatric population of 608,036, resulting in 1,824,107 PY (see baseline characteristics, Table 1). Consent was obtained from 216 cases in the IBSEN III study (flowchart in Figure S1). The distribution of diagnoses available for PIBD cases without consent did not differ significantly from the IBSEN III-included cases ($p = 0.27$).

We observed male predominance in the CD group (1.4:1) and slight female predominance in the UC group (1.1:1). The median age was 2.1 years lower for CD patients than for UC patients ($p = 0.002$). Thirty-two cases (14.8%) were classified as early-onset IBD, and 10 cases (4.6%) were classified as very early-onset IBD. None of the patients were younger than 2 years at diagnosis. Vitamin D, C-reactive protein (CRP), and platelets, as well as fecal calprotectin, differed significantly from the symptomatic controls (Table 1).

In 193 (89.4%) IBSEN III cases, biopsies were obtained from the terminal ileum, and in 175 (81%) cases, biopsies were obtained from the upper gastrointestinal tract. The endoscopist's tentative diagnosis of CD corresponded with the final diagnosis in 109 out of 118 cases (positive predictive value [PPV] 87.2% and; negative predictive value [NPV] 95.4%). However, the endoscopist overestimated UC with initially 87 cases compared to 78 confirmed cases (PPV 86.2%, NPV 98.7%, including three CD, eight IBDU, and one suspected IBD that was not confirmed). EIMs at diagnosis, defined as mucocutaneous, renal, hepatic, ocular, or articular diseases coexisting with PIBD, were observed in 2.3% but only found in the UC group. (Table 1) The median time from the first symptom to PIBD diagnosis was 2 months longer for CD patients compared to UC patients ($p < 0.01$).

The PIBD incidence rate was 17.8 per 100,000 (95% CI: 15.9–19.8). No significant change in the incidence of PIBD was observed during the 3-year study period (17.60, 17.90, and 17.78, respectively; $p = 0.99$). Table 2 presents the age-adjusted incidence rates of PIBD across the CD, UC, and IBDU subtypes, indicating that the incidence rises with age: UC incidence increases more than CD incidence, while IBDU exhibits a minor increase. The PIBD incidence rate is adjusted to European and World Standard populations in Supporting Information S2: Table S2.

Figure 1 shows the PIBD incidence development from the three IBSEN studies starting in 1990 and data gathered within the same geographical area. The age was adjusted to under 16 years in the studied periods to align with the inclusion age of the original IBSEN study. The figure illustrates a 2.8-fold increase in the incidence of PIBD from 4.7 to 13.6 per 105 PY, primarily contributed by CD patients. There was no overlap of confidence intervals between the first and the last study period, and the figure does not indicate any clear signs of a plateauing tendency in any of the diagnostic subgroups. The incidence of CD increased nonsignificantly more than that of UC from 1991 to 2019 ($p = 0.27$). A significantly higher CRP and platelets and lower BMI were found in IBSEN 1 compared to IBSEN III (Table 1), but other objective markers of severity were not available for comparison.

The most common CD location was ileocolonic disease, classified as L3 according to the Paris classification (Table 3). The ileocecal location (L1) was observed slightly more often in patients 10 years or older (23% vs. 17%, $p = 0.64$) (Table 3). A total of 47 patients (39.8%) had upper gastrointestinal tract involvement (L4), of which eight patients (6.8%) had L4 as the only disease distribution. Fifteen patients (12.8%) had perianal disease.

Impaired growth was reported in 45 patients (20.1%) at inclusion, but no significant difference was found between the CD and UC patients (25% and 15.4%, respectively; $p = 0.17$). The proportion of patients with stricturing, known in the Paris classification as behavior B2 or penetrating (B3) disease, increased with age (Table 3).

Pancolitis was the most common phenotype in UC (41%), with a distribution most pronounced among children under 10 years of age. (Table 3). Almost one-third (23/78) of the patients with UC presented with proctitis. Seven UC patients were diagnosed with severe disease last week before inclusion, while 16 patients (20.5%) had experienced severe disease before this time point (S2; PUCAI score >65).

A logistic regression was performed to ascertain the effects of a severe phenotype, as well as the child's sex, age, inheritance, body mass index, diagnostic delay, tonsillectomy, cesarean birth, breastfeeding, use of antibiotics in the last 3 months, NSAID use in the last month, CRP levels, Vitamin D levels, and thrombocyte levels on the likelihood that participants have growth retardation (Supporting Information S2: Table S3a–c). The logistic regression model was statistically significant, $\chi^2(4) = 12.7$, $p = 0.013$. The model explained 8.9% (Nagelkerke R^2) of the variance in growth retardation and correctly classified 79.6% of cases; however, except for the abbrivated PCDAI score, CRP and platelet count, no covariate variables contributed significantly to the risk of growth retardation.

TABLE 1 Baseline characteristics of incident IBD patients: All, included in the IBSEN III cohort, and symptomatic controls.

		PIBD		CD		UC		IBDU		Symptomatic control		IBSEN I	
PIBD in SE-Norway	*N* (%)	324		184	(56.8)	118	(36.4)	22	(6.8)				
IBSEN III included	*N* (%)	216	(100)	118	(54.6)	78	(36.1)	20	(9.3)	45		57	(100)
Age—years	Median (IQR)	14.8	(11.7–16.3)[c]	13.8[d]	(11.6–15.9)	15.9	(13.3–16.7)	13.3	(9.9–16.0)	12.5	(7.8–14.8)	15.3	(12.8–16.4)
Sex—male	*n* (%)	116	(53.7)	68	(57.8)	38	(48.7)	10	(50.0)	29	(64.4)	32	(56.1)
Onset <6 years VEOIBD	*n* (%)	10	(4.6)	5	(4.2)	3	(3.8)	2	(10)			2	(3.5)
Onset <10 years EOIBD	*n* (%)	32	(14.8)	18	(15.3)	9	(11.5)	5	(25.0)			6	(10.5)
1. degree family IBD	*n* (%)	19	(8.8)	13	(11.0	5	(6.4)	1	(5.0)	1	(2.3)	6	(10.5)
Body mass index (kg/m^2)		18.6[c]	(16.3–21.4)	18.3	(16.1–20.9)	19.0	(16.8–21.5)	19.3	(16.7–24.5)	17.1	(15.8–20.4)	17.3[e]	(15.8–20.4)
Growth delay	*n* (%)	45[c]	(20.8)	30	(25.4)	12	(15.4)	3	(15.0)	3	(6.7)	na	
Puberty delay[a]	*n* (%)	4	(2.6)	3	(2.5)	1	(1.6)	0	(0)	0	(0)	na	
EIMs	*n* (%)	5	(2.3)	0	(0)	5	(6.4)	0	(0)			na	
Diagnostic delay	Median (IQR)	6	(3.0–12.0)	7[d]	(3.0–13.0)	5	(2.0–6.25)	4	(2.3–11.3)	24	(11.5–60.0)	4[e]	(2.0–6.3)
PCDAI/PUCAI	Median (IQR)	.	.	15	(10–25)	30	(18.8–50.0)	32.5	(15.0–38.8)			na	
Other autoimmunity	*n* (%)	5	(2.3)	0	(0)	5	(6.4)	0	(0)	1	(2.3)	na	
Tonsillectomy	*n* (%)	18	(8.3)	13	(11.0)	4	(5.1)	1	(5.0)	7	(15.6)	na	
Appendectomy	*n* (%)	1	(0.5)	1	(0.8)	0	(0)	0	(0)	0	(0)	na	
Sectio	*n* (%)	17	12.4)	10	(12.5)	0	(11.4)	2	(10.0)	9	(27.3)	na	
Breastfed	*n* (%)	126	(92.6)	73	(91.3)	50	(93.0)	13	(65.0)	30	(85.7)	na	
Antibiotics last 3 months	*n* (%)	29	(13.5)	14	(11.9)	10	(12.8)	5	(26.3)	1	(2.2)	na	
NSAID last 1 month	*n* (%)	41	(19.1)	22	(18.6)	15	(19.2)	4	(20.0)	3	(7.1)	na	
Vitamin D nmol/L	Median (IQR)	56.0[c]	(44.0–70.0)	58.6[d]	(44.5–58.0)	51.0	(40.0–67.0)	61.0	(51.0–72.0)	64.0	(51.5–76.8)	na	
C-reactive protein mg/L	Median (IQR)	4.0[c]	(1.1–16.5)	5.0[d]	(2.8–23.1)	4.0	(1.0–9.0)	3.5	(1.0–6.0)	0.3	(0.0–2.0)	18[e]	(10–51)
Thrombocytes x10^9/L	Median (IQR)	353[c]	(287–425)	377	(305–438)	335	(274–404)	347	(277–451)	291	(243–356)	424[e]	(317–499)
Calprotectin[b] mg/kg	Median (IQR)	926.0[c]	(266–1801)	1801	(260–1801)	839	(245–1801)	737	(315.0–1801)	87	(45–127)	na	

Note: The historic IBSEN I is shown to the right.

Abbreviations: CD, Crohn's disease; EOIBD, early onset IBD; IBSEN III, Inflammatory Bowel Disease in South-Eastern Norway III; IQR, interquartile range; na, not available; PCDAI, pediatric Crohn's disease activity index; PIBD, pediatric inflammatory bowel disease; PUCAI, pediatric ulcerative colitis activity index; UC, ulcerative colitis; VEOIBD, very early onset IBD.

[a]Number and percent of the respondens in each category.

[b]Upper limit 1801.0 mg/kg.

[c]Statistical tests: PIBD versus symptomatic control $p \leq 0.05$.

[d]Statistical tests: CD versus UC group $p \leq 0.05$.

[e]Statistical tests: PIBD group versus IBSEN I group $p \leq 0.05$.

TABLE 2 Incidence of pediatric IBD in different age groups per 100,000 person-years.

Age in years	Cases (%)	Person years	PIBD	CD	UC	IBDU
VEO (<6) (95% CI)	15 (4.6)	554,721	2.7 (1.5–4.5)	1.4 (0.6–2.8)	0.9 (0.3–2.1)	0.4 (0.04–1.3)
EO (<10) (95% CI)	47 (14.5)	986,645	4.8 (3.5–6.3)	2.9 (2.0–4.2)	1.3 (0.7–2.3)	0.5 (0.2–1.2)
<15 years (95% CI)	174 (53.7)	1,511,801	11.5 (9.9–13.4)	7.4 (6.1–8.9)	3.2 (2.4–4.3)	0.9 (0.5–1.5)
<16 years (95% CI)	220 (67.9)	1,614,296	13.6 (11.9–15.6)	8.4 (7.0–9.9)	4.2 (3.3–5.3)	1.1 (0.6–1.7)
<17 years (95% CI)	272 (84.0)	1,718,074	15.8 (14.0–17.8)	9.2 (7.8–10.8)	5.5 (4.5–6.8)	1.1 (0.7–1.7)
<18 years (95% CI)	324 (100)	1,824,107	17.8 (15.9–19.8)	10.1 (8.7–11.7)	6.5 (5.4–7.8)	1.2 (0.76–1.8)

Abbreviations: CD, Crohn's disease; CI, confidence interval; EO, early onset; IBDU, inflammatory bowel disease unclassified; PIBD, pediatric inflammatory bowel disease; UC, ulcerative colitis; VEO, very early onset.

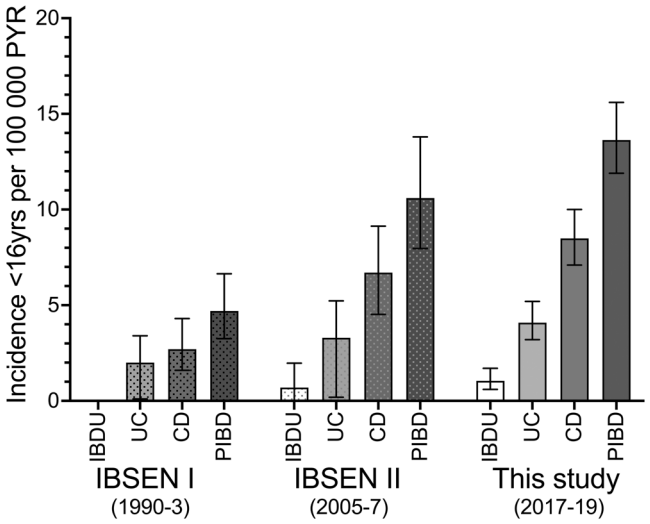

FIGURE 1 Pediatric IBD incidence in South-Eastern Norway from the IBSEN studies 1990–2019. Abbreviations: IBD, inflammatory bowel disease; IBSEN, Inflammatory Bowel Disease in South-Eastern Norway.

4 | DISCUSSION

This population-based cohort study indicated that the incidence of PIBD is high and is rising in South-Eastern Norway. This increase in incidence, compared to two prior pediatric cohort studies covering the same geographical area, appeared to be driven by an increase in ulcerative proctitis and terminal ileitis.

Nordic countries have reported a high incidence of PIBD in the recent decades. (Supporting Information S2: Table S4).[3,24–29] A shared genetic risk in the Nordic populations as the main explanation for this high incidence seems unlikely, given the substantial changes over a few decades. There were also notable differences in PIBD phenotypes among Nordic countries (Supporting Information S2: Table S5).[12,28,30] An increasing incidence by latitude has been shown in a recent register-based nationwide study on PIBD in Norway and further demonstrated in studies from Finland and North America.[31–33] The median age at diagnosis varied between studies on PIBD, even when the inclusion age was consistent (Supporting Information S2: Table S5).[34–37] This may partly explain the differences in the incidence and distribution of the PIBD phenotypes. Potential environmental risk factors, such as a Westernized diet, early antibiotic use, hygiene, and living conditions in South-Eastern Norway, are likely similar to those in other Nordic countries.[38] Ongoing studies from this and other Nordic IBD cohort studies explore infections, antibiotic use, diet, other lifestyle factors, and psychosocial aspects.[2,39,40]

From the first IBSEN study, the reported PIBD incidence has increased from 4.7 (95% CI: 3.3–6.6) to 13.6 (95% CI: 11.9–15.6) in children and adolescents under 16 (Figure 1). A plateauing trend of incidence in children has been hypothesized based on the theory of the four epidemiological stages of IBD.[41] Adult data from the last decade indicate that Western countries have reached the period of compounding prevalence, where the incidence stabilizes, and the prevalence continues to increase since IBD.[42] The life expectancy for children in Western countries is approximately 80 years, and PIBD is a chronic disease with no cure currently available; the prevalence in this population is expected to increase significantly. A few pediatric studies have shown a plateauing development in incidence.[26,32,37] A study from Iceland showed a plateauing incidence of 5.6 per 100,000 among individuals under 16 years of age, while an Italian multicenter study stabilized at 1.8 per 100,000 for patients under 18.[26,37] However, the number of cases was either low or not population-based, which affects the conclusion. Importantly, our data do not support this finding; we demonstrate an increase within the same geographical area studied since 1990, suggesting that differences in population characteristics are unlikely explanations. Most European and Canadian studies on PIBD incidence, including a recent Danish study, have also shown an increasing incidence.[3,12,43] An ongoing rise in PIBD incidence may have several causes. The availability and use of diagnostic tools, such as fecal

TABLE 3 Location and behavior of pediatric Crohn's disease and ulcerative colitis in South-Eastern Norway according to the Paris classification.

	Age <10 years (A1a)		Age ≥10 <17 years (A1b)		Age <18 years	
	n = 18	(%)	*n* = 88	(%)	*n* = 118	(%)
CD location (L)						
L1 (ileal + limited cecal)	3	17	20	23	26	22
L2 (colonic)	3	17	19	22	24	20
L3 (ileocolonic)	9	50	40	45	56	47
L4 isolated (upper GI)	1	6	7	8	8	7
L4a + L1–3 (proximal to Treitz)	3	17	26	24	34	29
L4b + L1–3 (distal to Treitz)	0	0	4	6	5	4
Missing	2	11	2	2	4	3
CD behavior (B)						
B1 (nonstrictur/penetrating)	14	77	68	77	91	77
B2 (stricturing)	1	6	14	16	16	14
B3 (penetrating)	0	0	2	2	4	3
B2 + B3	0	0	1	1	1	1
Missing	3	17	3	3	6	5
Perianal disease	2	11	10	11	15	13
G1 (growth) (%)	1	5.5	21	24	24	20
	n = 9	(%)	*n* = 54	%	*n* = 78	%
UC extension (E)						
E1 (ulcerative proctitis)	2	22	21	39	23	29
E2 (left sided, splenic flex)	1	11	10	19	12	15
E3 (extensive, hepatic flex)	1	11	8	15	11	14
E4 (pancolitis)	5	56	15	28	32	41
UC severity (S)						
S0 (never severe)	7	78	43	80	62	79
S1 (ever severe) (PUCAI ≥65)	2	22	11	20	16	21

Abbreviations: CD, Crohn's disease; PUCAI, pediatric ulcerative colitis activity index; UC, ulcerative colitis.

calprotectin, have increased alongside the incidence of PIBD since the first IBSEN study. This may explain a temporary increase in incidence due to the detection of more subtle PIBD cases. Additionally, since nearly 10 percent of the pediatric population in our database comes from immigrant families, the immigration of workers and families from low PIBD incidence countries in Asia to South-Eastern Norway in the 1970s may have temporarily decreased the incidence observed in the first IBSEN study.[44] Ongoing environmental, lifestyle, and health-related risk factors for IBD may affect different age groups in distinct ways, such as smoking habits or the use of antibiotics before and after early childhood.[45] In summary, this may explain a continued increase in PIBD incidence while the adult incidence stabilizes.

To our knowledge, phenotypic comparisons with earlier studies within a specific region have yet to be performed. The phenotype distribution from the current IBSEN III study is comparable to that of other extensive population studies reporting PIBD phenotypes when age groups were adjusted to <18 years or <16 years (Supporting Information S2: Table S5).[4,10,34–37,46,47]

To fully explore the phenotypes, we documented a high proportion of complete investigations, including upper endoscopy and magnetic resonance imaging (MRI), which may explain the 40% rate of upper gastrointestinal disease (GI). The former IBSEN II study reported an even higher detection rate (76%); however, histologically, 44.4% were CD-specific, which aligns with our findings.[29] Upper GI disease was reported in 0.4% of

cases in a Hungarian study, but up to 46% in the EUROKIDS study. Different definitions of CD lesions (erosions, aphthous ulcers, or granulomas) or whether the upper GI (L4) definition encompasses or omits the combined, isolated, or total L4 distribution may explain these differences. The number of ileal (L1) phenotypes was almost doubled in our study compared with previous IBSEN studies, reporting a lower proportion of ileocolonic (L3) phenotypes in the IBSEN II study and a reduced ratio of colonic (L2) phenotypes in the first IBSEN study. Two recent studies from Canada and Italy also reported a high proportion of ileal (L1) phenotypes (20% and 26%, respectively), and two Nordic studies with PIBD diagnoses before 2008 reported low proportions of ileocolonic distribution (L3) (Supporting Information S2: Table S5). In contrast, one Swedish study reported low ileal L1 (9%) and high colonic (L2) (75%). This is interesting, as most recent pediatric studies have reported ileocolonic distribution (L3) as the more common phenotype.[4,10,37,47] The increased availability of capsule endoscopy and MRI may explain some of the changes in the phenotype ratios. Taken together, it is more likely to indicate development toward more proximal disease progression.

Conversely, in UC, the phenotypes identified in the IBSEN studies have shifted toward the distal part of the GI tract: proctitis, classified as E1 in the Paris classification and accounting for almost one-third of the cases in our study. Moreover, 55% of with UC patients have extensive or pancolitis (E3 + E4) phenotypes, a decrease from the original IBSEN study. A high proportion of extensive and pancolitis distribution in pediatric compared to adult series is well-documented.[48] In line with our findings, a comprehensive EPIMAD study from Northern France reported in pediatric patients a 29% left-sided (E2) and a 28% proctitis (E1) disease location.[46] A surveillance bias cannot be ruled out as the increased proportion of proctitis may be explained by an early diagnosis of (the more adult type) UC from better and more available calprotectin tests and specialist care. However, the increased total number of UCs observed may also suggest a genuine increase in proctitis (E1).

The severity of symptoms or complications is an essential aspect of PIBD. In the present study, 18% of CD patients experienced stricturing and/or penetrating complications, whereas 21% of UC patients had experienced severe disease as assessed by an abbreviated PUCAI score (Table 3). The rate of complicated CD disease is comparable to two population-based studies from Hungary (15%), the French EPIMAD study (22%) and the multicenter EUROKIDS study (18%).[34,36,46] The relative complication rate was reported lower in a Swedish population-based study (6%) and a register study from Canada (13%), and may partly be explained by lower inclusion age (<16 and <17 years, respectively).[10,47] However, when adjusting the inclusion age to <16 years in the present study, the complication rate in CD was still high at 17.3%.

Few studies have integrated a disease activity score or severity score along with the description of the phenotype extension (E) or localization (L) of PIBD. These are referred to in Supporting Information S2: Table S5, but they employ various scores, including the global assessment score, as well as different variants or parts of the pediatric activity indexes (PUCAI and PCDAI), a disabling score, or no score at all, which makes comparisons between studies challenging. Inclusion age does also affect the abbrivated PCDAI and the PUCAI scores (Supporting Information S2: Tables S7 and S9). Similarly, severity scores have evolved between the original IBSEN and IBSEN III (see Supporting Information S2: Tables S6 and S8). Still, in the IBSEN studies, blood tests like CRP and platelet count show significant changes from the first to the last IBSEN study, indicating a lesser inflammatory load in the IBSEN III patients, who also show a more limited extension of the disease in the colon (Supporting Information S2: Table S5). The original IBSEN study did not utilize fecal calprotectin, another essential inflammatory marker, nor did the other studies on PIBD phenotypes supplement their phenotype descriptions with data on this inflammation marker.

The main strength of our study is its population-based design involving unselected treatment-naïve patients with PIBD, combined with more than 25 years of detailed knowledge about PIBD epidemiology in this well-defined geographical area. Furthermore, the high completeness of endoscopy and imaging supporting phenotype definition is an additional advantage. A limitation was that only two-thirds of the identified patients with PIBD were included in the IBSEN III study. A well-known challenge is to include consent rather than an anonymous registry, in addition to the obstacles of involving many centers and doctors/nurses. The IBSEN studies are similar, but not exactly comparable due to the lower number of participating hospitals in the first two IBSEN studies; all hospitals from the South-Eastern region, however, were included in the IBSEN III study. The studies were separated by 12 and 9 years, respectively; in this sense, they were not wholly independent populations. In addition, the consent practice for inclusion has changed over time. As 9.3% of the included patients were classified as having IBDU (see Figure 1) and 21 patients were excluded as they did meet some but not all diagnostic criteria (see flowchart Figure S1), this may have resulted in an underestimation of the true incidence of CD and UC. There were no registered EIMs in CD patients, which may be caused by registration failure, as the expected proportion of EIMs among pediatric CD patients is 20%–30% in other studies, and the risk of inclusion bias or exclusion of pediatric CD patients with EIMs is considered low.[49] In addition, a more limited diagnostic "drift" from CD to UC and vice versa is expected.[50]

In conclusion, we documented a high and increasing incidence of PIBD in a population-based inception cohort of unselected pediatric patients from South-Eastern Norway. Phenotypes that are more typical of adult IBD, such as terminal ileitis and proctitis, are driving the rising incidence. Further research on specific IBD phenotypes may enhance our understanding of their etiology and prevention factors.

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CONFLICTS OF INTEREST STATEMENT

Svend Andersen received a travel fund from Ferring Pharma. Vendel A. Kristensen: Takeda (consultant + advisory board), Tillotts Pharma (advisory board), Janssen-Cilag (consultant), and Thermo Fisher Scientific (speaker). Marte Lie Høivik: Investigator-initiated research grants from Takeda, Pfizer, Tilllotts, Ferring, and Janssen. Speaker honoraria from Takeda, Tillotts, Ferring, AbbVie, Galapagos, and Meda. Advisory boards Takeda, Galapagos, MSD, Lilly, and AbbVie. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the privacy of the individuals who participated in the study. However, the data can be shared with research groups upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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