Inflammatory Bowel Diseases, 2025, **31**, 87–94
https://doi.org/10.1093/ibd/izae047
Advance access publication 20 March 2024
Original Research Article - Clinical

Children and Adolescents Diagnosed With Inflammatory Bowel Disease Are at Increased Risk of Developing Diseases With a Possible Autoimmune Pathogenesis

Line Riis Jølving, PhD,[*,†] Floor Dijkstra Zegers, MSc,[*] Ken Lund, PhD,[*,†] Mette Wod, PhD,[*,†] Jan Nielsen, PhD,[*,†] Niels Qvist, DMSc,[‡,§,¶] Rasmus Gaardskær Nielsen, PhD,[¶,‖] and Bente Mertz Nørgård, DMSc[*,†]

[*]Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark
[†]Research Unit of Clinical Epidemiology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[‡]Research Unit for Surgery and Center for IBD Care, Odense University Hospital, Odense, Denmark
[§]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[¶]Centre of Excellence in Gastrointestinal Diseases and Malformations in Infancy and Childhood (GAIN), Odense University Hospital, Odense, Denmark
[‖]Hans Christian Andersen Children's Hospital, Odense University Hospital, and Research Unit of Pediatrics, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Address correspondence to: Line Riis Jølving, Center for Clinical Epidemiology, Odense University Hospital, Kløvervænget 30, entrance 216, DK-5000 Odense, Denmark. Tel: +45 2115 3599 (line.joelving@rsyd.dk).

Background: The development of diseases with a possible autoimmune pathogenesis is common in adults with inflammatory bowel disease (IBD). In early onset IBD, it may differ but the evidence is sparse. We aimed to investigate the risk and time span from IBD diagnosis to outcomes with different associated disorders with possible autoimmune pathogenesis.

Methods: A register-based study included all Danish patients with early onset of IBD (≤18 years) between 1980 and 2021 and 50 matched references without IBD for each case. We examined the risk of type 1 and type 2 diabetes, celiac disease, thyroid disease, rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis in Cox regression models.

Results: In total, 6822 patients with IBD were identified, and 337 728 matched references. The median age at the time of IBD diagnosis or index date for the matched references was 16 years (25-75 percentile: 13-18 years), and the median age at the time of an outcome or at the end of follow-up was 28.1 years (25-75 percentile: 21.5-37.0 years). According to the cumulative incidence plots psoriatic arthritis, and spondyloarthritis was diagnosed approximately 10 years after the IBD onset, and the remaining outcomes later. The adjusted hazard ratio after full follow-up was 4.72 (95% CI, 3.85-5.80) for psoriatic arthritis, 5.21 (95% CI, 4.17-6.50) for spondyloarthritis, 2.77 (95% CI, 1.92-4.00) for celiac disease, 2.15 (95% CI, 1.54-3.01) for rheumatoid arthritis, 1.69 (95% CI, 1.23-2.32) and 1.64 (95% CI, 1.21-2.21) for type 1 and type 2 diabetes, respectively. For thyroid disease, it was 1.16 (95% CI, 0.97-1.40).

Conclusions: The risk estimates were significantly increased for all outcomes at the end of follow-up, except for thyroid disease, but according to the cumulative incidence plots, only psoriatic arthritis and spondyloarthritis occurred earlier in the IBD cohort than in the matched references.

Lay Summary

Children and adolescents diagnosed with inflammatory bowel disease are at increased risk of developing several diseases with possible autoimmune pathogenesis compared with a matched reference group. Cumulative incidence curves showed that psoriatic arthritis and spondyloarthritis debut in young adulthood when compared with a matched reference group without IBD.

Key Words: ulcerative colitis, Crohn's disease, early onset IBD, autoimmune diseases, cohort study

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that covers ulcerative colitis and Crohn's disease. The etiology of IBD is partly unknown. The pathogenesis is multifactorial including a dysregulated immune response, epithelial barrier defects, environmental factors, and genetic inherence.[1] Inflammatory bowel disease in childhood and adolescence constitutes 10% to 25% of all patients with IBD,[2-4] with an increasing incidence.[5-8] Early onset IBD is characterized by a more advanced disease at the time of diagnosis,[9,10] a phenotype of a more aggressive disease,[11-13] and increased use of immunomodulatory therapies compared with patients with debut in adulthood.[14] The association between adult IBD and other diseases with possible autoimmune pathogenesis is well described in the literature and occurs in up to 50% of the adult population of patients with IBD.[15-19] Information on the development of these conditions after early onset IBD may add important

Received for publication: November 8, 2023. Editorial Decision: February 21, 2024

Key Messages

• What is already known?

Diagnosis with IBD is associated with an increased risk of developing different autoimmune diseases in adults.

• What is new here?

Based on a nationwide cohort of children and adolescents with IBD (≤18 years of age), our study suggests an increased risk of psoriatic arthritis and spondyloarthritis already 10 years after onset compared with matched references.

• How can this study help patient care?

The findings of the study should enable clinical awareness to identify the coincidence of other diseases with possible autoimmune pathogenesis in patients with early onset IBD, especially psoriatic arthritis and spondyloarthritis.

knowledge to a possible difference in the etiology and/or pathogenesis in pediatric vs adult onset IBD. In addition, the awareness of the coexisting diseases is important for clinical practice, as they may be an indicator of IBD disease severity and lead to an intensified need for medical and surgical treatment and may negatively affect the quality of life in patients with IBD.[20]

Musculoskeletal disorders are the most commonly associated autoimmune diseases, and celiac disease is the most common disease in the gastrointestinal tract. Diabetes type 1 and thyroid diseases are the most common endocrinological diseases. Although type 2 diabetes is not an established autoimmune disorder, we chose to include this because it may have potential links to immune cell dysfunction.[21,22]

In this cohort study, we examined the risk and timing of developing some of the most frequent chronic diseases with possible autoimmune pathogenesis in terms of a diagnosis with diabetes, celiac disease, thyroid disease, rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis in patients diagnosed with IBD at 18 years or younger, usually attending children departments in Denmark compared with matched references from the general population.

Material and Methods

Data Sources/Setting

This was a population-based matched cohort study using the nationwide Danish health registries. The Danish population includes approximately 5.8 million people, and all inhabitants have free access to the tax-financed healthcare system. We used data from (1) the Danish National Patient Register and (2) the Danish Civil Register. Since 1977, the Danish National Patient Register has provided data on diagnoses from any Danish hospital using the International Classification of Disease (ICD), with the ICD-8 classification from 1977 to 1993, and the ICD-10 classification from 1994 and onwards. The Danish Civil Register provides information on the time of birth, sex, death, and migration for all citizens in Denmark and includes the unique 10-digit civil registration number that makes an unambiguous record linkage between all registries possible, including linkage between children and their parents.

Study Population

The study population consists of all Danish children and adolescents with a diagnosis of IBD (≤18 years) from 1980 to November 2021 and their sex and age-matched references without IBD.[23] A diagnostic delay in IBD is very common, and therefore we chose to include participants with an age below or equal to 18 years.

Cohort With Early Onset IBD

The inclusion criteria were at least 2 diagnostic codes for valid registration of either ulcerative colitis or Crohn's disease.[24] The diagnosis was identified in the Danish National Patient Register for ulcerative colitis (ICD-8: 563.19; 569.04 and ICD-10: K51) and for Crohn's disease (ICD-8: 563.01 and ICD-10: K50). The date of the diagnosis of IBD was the first occurrence of a registered diagnostic code, and it defined the index date, whereas the latter diagnosis (ulcerative colitis or Crohn's disease) defined the specific type of IBD used in the stratified analysis. If any of the children had the outcome of interest before the index date, the patient and the matched references were not included.

Cohort of Matched References Without IBD

The cohort with matched references was randomly selected from the general population using the Danish Civil Registration System. For every patient with early onset IBD, 50 children without IBD were matched on sex, year, and month of birth (1:50). The references should be alive on the index date and live in Denmark. We used risk set sampling when selecting the references to match patients with IBD.[25] If any of the references were diagnosed with IBD after their matching, they remained references through follow-up (n = 416, 0.12%).

Outcome Ascertainment

The following outcomes were examined in both cohorts: (1) type 1 diabetes (ICD-8: 249, with all subgroups, and ICD-10: E10), (2) type 2 diabetes (ICD-8: 250 with all subgroups, and ICD-10: E11), (3) celiac disease (ICD-8: 269.00 and ICD-10: K90.0), (4) thyroid diseases (ICD-8: 240 with all subgroups, 241 with all subgroups, 242 with all subgroups, 243 with all subgroups, 244 with all subgroups, 245.02, 245.03, 245.04, 245.08, 246 with all subgroups, and ICD-10: E00-E07), (5) rheumatoid arthritis (ICD-8: 712.19, 712.29, 712.39, 712.59, and 712.09 and ICD-10: M05 with all subgroups, M06 with all subgroups, and M08 with all subgroups), (6) psoriatic arthritis, (ICD-8: 696.09, 696.10, and 696.19, and ICD-10: L40 with all subgroups, M07.0-M07.3), and (7) spondyloarthritis (ICD-8: 712.49. ICD-10: M45.9-M46 with all subgroups). For a valid assessment of the outcomes, we required at least 2 registered diagnoses of the specific outcomes after the index date. For each patient, it was possible to have more than 1 outcome. In the case of a patient having more than 1 outcome during follow-up, the date of the first registration was used in the statistical model. All outcomes were analyzed separately.

Data on Covariates

Potential confounders were selected a priori and included maternal and paternal diseases identical to the offspring outcomes (eg, when estimating the risk of diabetes type 1 in a child, we adjusted for maternal or paternal underlying diabetes type 1). The disease history of the parents was established using the

Danish National Patient Register, and for a parent to have a specific underlying disease, we also required at least 2 registered diagnoses occurring before the date of birth of the child.

Statistical Analysis

The characteristics of the cohort with early onset IBD and the matched references were calculated. The association between early onset IBD and incident disease was estimated using a Cox proportional hazard regression model with survival time analysis of the hazard ratios (HRs) with the corresponding 95% confidence interval (95% CI). We provided risk estimates for the patients with IBD relative to the matched references according to each outcome using the sandwich estimator clustered on the same set of parents.[26] The proportional hazards assumption was assessed visually using Schoenfeld residuals. Additionally, we stratified the analysis on IBD subtypes (ie, ulcerative colitis or Crohn's disease). The follow-up time began on the index date and continued until the first occurrence of an outcome, emigration from Denmark or death, whichever came first. Moreover, the cumulative incidences were plotted for a visual comparison of the different outcomes of interest after the diagnosis of IBD or the index date between the 2 cohorts.

Patient and Public Involvement

Patients and relative representatives are part of the research council at our department and have been involved in parts of this research process, in which they have contributed to important discussions about the study idea and which outcomes to measure. The representatives were involved in neither the study design, the analyses, nor the manuscript writing.

Results

Characteristics of Patients and the Cohort of Matched References

We identified a total of 6822 patients with early onset IBD and 337 728 age- and sex-matched references, where 51.2% were females. Approximately half of the patients were diagnosed with IBD in the period from 2010 and onwards (44.8%). More than 90% of the patients with early onset IBD were older than 10 years at the time of the first diagnosis. The median age at IBD diagnosis was 16 years (25-75 percentile, 13-18 years), and the median age at the time of an outcome or at end of follow-up was 28.1 years (25-75 percentile, 21.5-37.0) in the overall group, 28.1 (25-75 percentile, 21.5-36.9) in the early onset IBD cohort, and 28.2 (25-75 percentile, 21.5-37.1) in the reference cohort. The characteristics of the 2 cohorts are presented in Table 1, along with data on parental diseases diagnosed before the birth of the offspring in the 2 cohorts. The number of patients diagnosed at the age of 10 or younger was low and even lower for children below the age of 6 years (not shown). Therefore, we were not able to perform a subanalysis of children with very early onset IBD.

Table 1. Patient characteristics of children with early onset inflammatory bowel disease (IBD) diagnosed from January 1, 1980, to November 22, 2021, and their matched references without IBD at the index date.

	Cohort of Patients With Early Onset IBD, N = 6822	Cohort of Matched References, N = 337 728
Median age at first IBD diagnosis (25-75 percentile)		
Years	16 (13-18)	16 (13-18)
Age at first IBD diagnosis (%)		
< 10 years	649 (9.5)	32 215 (9.5)
≥ 10 years	6173 (90.5)	305 513 (90.5)
Sex (%)		
Female	3491 (51.2)	172 540 (51.1)
Male	3331 (48.8)	165 188 (48.9)
Calendar year at IBD diagnosis/index date (%)		
1980-1989	666 (9.8)	33 210 (9.8)
1990-1999	1147 (16.8)	57 042 (16.9)
2000-2009	1955 (28.7)	96 876 (28.7)
≥2010	3054 (44.8)	150 600 (44.6)
IBD subtype (%)		
Ulcerative colitis	3292 (48.3)	
Crohn's disease	3530 (51.7)	
Maternal diseases before childbirth (%)		
Diabetes type 1	11 (0.2)	567 (0.2)
Diabetes type 2	12 (0.2)	589 (0.2)
Celiac disease	0 (0.0)	44 (0.0)
Thyroid disease	37 (0.5)	1607 (0.5)
Rheumatoid arthritis	2 (0.0)	183 (0.1)
Psoriatic arthritis	2 (0.0)	126 (0.0)
Spondyloarthritis	2 (0.0)	43 (0.0)
Ulcerative colitis	103 (1.5)	943 (0.3)
Crohn's disease	73 (1.1)	534 (0.2)
Paternal diseases before childbirth (%)		
Diabetes type 1	18 (0.3)	722 (0.2)
Diabetes type 2	12 (0.2)	571 (0.2)
Celiac disease	1 (0.0)	15 (0.0)
Thyroid disease	3 (0.0)	205 (0.1)
Rheumatoid arthritis	3 (0.0)	86 (0.0)
Psoriatic arthritis	5 (0.1)	102 (0.0)
Spondyloarthritis	7 (0.1)	87 (0.0)
Ulcerative colitis	87 (1.3)	800 (0.2)
Crohn's disease	52 (0.8)	384 (0.1)

Risk Estimates

The crude and adjusted HRs for the association between early onset IBD and the outcome diseases are presented in Table 2. The adjusted HR for patients with early onset IBD for type 1 and type 2 diabetes was 1.69 (95% CI, 1.23-2.32) and 1.64 (95% CI, 1.21-2.21), respectively compared with the matched references. The adjusted HR for celiac disease was 2.77 (95% CI, 1.92-4.00), rheumatoid arthritis 2.15 (95% CI, 1.54-3.01), psoriatic arthritis 4.72 (95% CI, 3.85-5.80), spondyloarthritis 5.21 (95% CI, 4.17-6.50), and thyroid disease 1.16 (95% CI, 0.97-1.40) compared with the matched references. Stratified on the IBD subtype, the adjusted HRs showed statistically significant increase for all outcomes in ulcerative colitis (Table 3), and for all outcomes in Crohn's disease with the exception of type 1 and type 2 diabetes and thyroid disease (Table 4).

Table 2. The crude and the adjusted hazard ratios (HRs) of autoimmune diseases in patients with early onset inflammatory bowel disease (IBD) and their matched references.

Disease	Cohort of Patients With Early Onset IBD		Cohort of Matched References		Hazard Ratios (95% CI)	
	Event, N	Time at Risk in Years	Events, N	Time at Risk in Years	Crude HR (95% CI)	Adjusted HR* (95% CI)
Diabetes type 1	41	203 836	1154	10 146 640	1.70 (1.24-2.32)	1.69 (1.23-2.32)
Diabetes type 2	43	204 100	1299	10 148 364	1.65 (1.22-2.23)	1.64 (1.21-2.21)
Celiac disease	37	204 050	529	10 156 341	2.77 (1.92-3.99)	2.77 (1.92-4.00)
Thyroid disease	113	203 420	4773	10 120 335	1.16 (0.97-1.40)	1.16 (0.97-1.40)
Rheumatoid arthritis	35	204 030	784	10 151 911	2.15 (1.54-3.01)	2.15 (1.54-3.01)
Psoriatic arthritis	92	203 765	985	10 151 529	4.74 (3.86-5.82)	4.72 (3.85-5.80)
Spondyloarthritis	81	203 692	774	10 153 720	5.19 (4.16-6.47)	5.21 (4.17-6.50)

*Adjusted for parental diagnoses with the same disease outcome (eg, outcome diabetes type 1 is adjusted for maternal and paternal diabetes type 1).

Table 3. The crude and the adjusted hazard ratios (HRs) of autoimmune diseases in patients with early onset ulcerative colitis (UC) and their matched references.

Disease	Cohort of Patients With Early Onset UC		Cohort of Matched References		Hazard Ratios (95% CI)	
	Events, N	Time at Risk in Years	Events, N	Time at Risk in Years	Crude HR (95% CI)	Adjusted HR* (95% CI)
Diabetes type 1	25	100 408	553	5 004 537	2.18 (1.46-3.25)	2.20 (1.48-3.28)
Diabetes type 2	29	100 528	659	5 005 080	2.19 (1.51-3.17)	2.18 (1.50-3.16)
Celiac disease	14	100 588	261	5 009 083	2.12 (1.17-3.83)	2.12 (1.17-3.82)
Thyroid disease	66	100 207	2,451	4 990 566	1.32 (1.04-1.69)	1.32 (1.04-1.69)
Rheumatoid arthritis	16	100 525	381	5 006 843	1.93 (1.16-3.20)	1.92 (1.16-3.19)
Psoriatic arthritis	27	100 483	475	5 006 977	2.85 (1.95-4.16)	2.86 (1.96-4.17)
Spondyloarthritis	35	100 449	407	5 007 633	4.37 (3.13-6.09)	4.37 (3.13-6.09)

*Adjusted for parental diagnoses with the same disease outcome eg, outcome diabetes type 1 is adjusted for maternal and paternal diabetes type 1.

Table 4. The crude and the adjusted hazard ratios (HRs) of autoimmune diseases in patients with early onset Crohn's disease (CD) and their matched references.

Disease	Cohort of patients With Early Onset CD		Cohort of Matched References		Hazard Ratios (95% CI)	
	Events, N	Time at Risk in Years	Events, N	Time at Risk in Years	Crude HR (95% CI)	Adjusted HR* (95% CI)
Diabetes type 1	16	103 428	601	5 142 103	1.25 (0.75-2.07)	1.26 (0.76-2.09)
Diabetes type 2	14	103 572	640	5 143 285	1.10 (0.65-1.86)	1.09 (0.65-1.84)
Celiac disease	23	103 462	268	5 147 259	3.41 (2.14-5.43)	3.42 (2.15-5.45)
Thyroid disease	47	103 214	2322	5 129 769	1.00 (0.75-1.32)	1.00 (0.75-1.32)
Rheumatoid arthritis	19	103 505	403	5 145 069	2.37 (1.51-3.71)	2.37 (1.51-3.71)
Psoriatic arthritis	65	103 282	510	5 144 553	6.54 (5.11-8.37)	6.51 (5.09-8.32)
Spondyloarthritis	46	103 243	367	5 146 088	6.07 (4.51-8.17)	6.12 (4.54-8.24)

*Adjusted for parental diagnoses with the same disease outcome eg, outcome diabetes type 1 is adjusted for maternal and paternal diabetes type 1.

Figure 1 shows the time in years from IBD diagnosis or matching (index date) to the diagnosis of any of the 7 examined outcomes during follow-up in the 2 cohorts. Compared with references, patients with early onset IBD had a short time interval (approximately 10 years) to the increase in the appearance of the outcome diagnoses with psoriatic arthritis and spondyloarthritis. The risk estimates were significantly increased for all outcomes at the end of follow-up, but according to the cumulative incidence plots, only psoriatic arthritis and spondyloarthritis occurred earlier in the IBD cohort than in the matched references. For rheumatoid arthritis, celiac disease, type 1 and type 2 diabetes, and thyroid disease, the figures showed that the diseases occurred over 20 years after the IBD diagnoses.

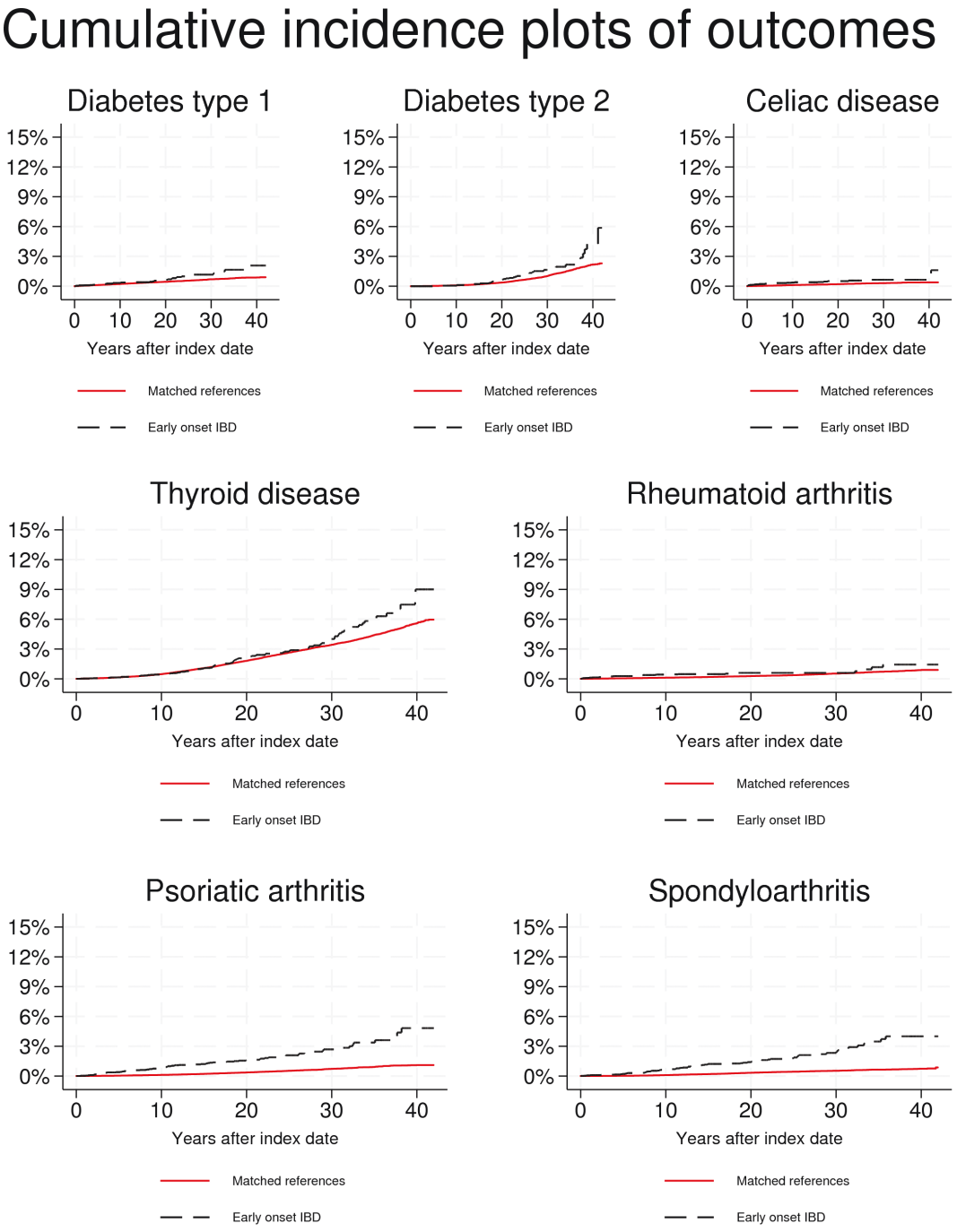

Figure 1. Cumulative incidence plots of outcomes.

Discussion

The main findings of our nationwide study on all patients with early onset IBD were that early onset IBD is associated with an increased risk of having a diagnosis with different diseases with a possible autoimmune pathogenesis at full follow-up. However, the visualization of the risk by the cumulative incidence plots showed that the increase was most pronounced in psoriatic arthritis and spondyloarthritis, approximately 10 years after the IBD diagnosis. The diagnosis of the remaining 5 outcomes occurred within a considerably longer time perspective.

The association between adult IBD and other diseases with possible autoimmune pathogenesis is well described in the literature.[15,16,27,28] Psoriatic arthritis may thus be increased in a population of patients with IBD when compared with the general population.[29] Our study suggests not only an adjusted HR of 4.72 (95% CI, 3.85-5.80) at end of follow-up but also that an increase may occur within few years after IBD diagnose. The inverse link between IBD and spondyloarthritis in adults has previously been described, where 6% to 14% of the patients with spondyloarthritis also had IBD in an adult study population.[30] This is also in accordance with our findings of a 5-fold increase compared with the references and in line with

our stratified estimates that the elevated increase has been most pronounced in patients with Crohn's disease in other studies.[29] In a meta-analysis on the risk of cooccurrence of rheumatoid arthritis in patients with IBD, an increased risk was found (2.59; 95% CI, 1.93-3.48) for CD. The risk remained significantly increased in both pediatric and adult patients, but for UC the risk was less significant in the pediatric group.[31] This is in line with the results from the present study where the adjusted HR for rheumatoid arthritis was 1.92 (95% CI, 1.16-3.19) for UC and 2.37 (95% CI, 1.51-3.71) for CD. This and the other differences between the UC and CD subgroup found in our study may indicate differences in the pathogenesis of the 2 different diseases. In 2 recent meta-analyses, an increased risk of celiac disease was reported, with a relative risk of 3.96 (95% CI, 2.23-7.02) and an odds ratio of 2.23 (95% CI, 1.99-2.50) comparable to the findings in our study. An inverse association with an increased risk of IBD in patients with primarily diagnosed celiac disease has also been described.[32,33]

An increase in both type 1 and type 2 diabetes occurred in the adjusted risk estimates with a delay of approximately 4 decades after the early IBD diagnosis in the present study. A population-based cohort study in adults above the age of 30 years from Denmark[27] showed an increased risk of type 2 diabetes both in patients with UC or CD, with the highest risk during recent calendar years compared with earlier times. The authors interpreted this result as a possible effect of changes in medical therapy. An analysis of the risk in different time periods was not performed in our study, but the long-time interval from diagnosis of IBD to the development of diabetes in the cumulative incidence plots may be confirmatory or be related to surveillance bias in patients with IBD.

Our study has several strengths. The nationwide health registers enable us to conduct large population-based observational studies using real-world data with no loss to follow-up. The diagnoses regarding both the exposure, parental diagnosis, and the outcomes are provided independently from the study question preventing information bias. A study from Sweden showed a positive predictive value of early onset IBD diagnosis of 93% (95% CI, 89-96) using at least 2 diagnostic codes from the national patient register.[24] We used an identical stringent approach in order to secure the robustness of the diagnoses related to the exposure. The information on maternal and paternal diseases was used as a surrogate marker for heredity and the genetic disease burden related to IBD,[34,35] and we were able to adjust for potentially hereditary diseases. Based on the clinical registrations, the health registers are known to hold high validity both in general[36] and high validity regarding disease-specific diagnoses surveillance[37-41] such as those applied as outcome diagnoses in our study, where 2 consecutive diagnoses were required.

This study also has limitations. It must be acknowledged that a potential bias of diagnosing less severe outcomes may be present in patients with early onset IBD due to increased medical awareness. Patients with IBD may experience other clinical symptoms from the gut, joints, and connective tissues prior to the diagnosis of IBD.[18,42-45] These symptoms are estimated to be present in 18% to 25% of all pediatric-onset IBD cases.[46-48] We examined the risk of disorders with possible autoimmune pathogenesis in patients with manifest IBD, and we only included outcome diagnoses registered after the diagnosis with IBD or at the corresponding time of matching in the reference group, acknowledging the timing aspects. Furthermore, as we only included outcomes with at least 2 registered diagnosis, we may in fact have underestimated the risks. We chose not to exclude individuals in the matched reference group with a later diagnosis of IBD because this might introduce a possible selection bias. Other family history such as sibling's disease history might have been relevant as a potential genetic impact of disease occurrence. However, we did not have access to these data.

Another limitation is that we did not measure a potential change in IBD diagnosis or disease activity during the observation period. The number of outcomes of the different disease-specific groups was small, and this limited statistical precision must be kept in mind when the results are interpreted. Since our study is based on hospital discharge records, it may represent more severe cases as we did not include diagnoses obtained from the general practitioners or from outpatient clinics before 1995. Finally, as in other observational studies, we cannot rule out the role of potential residual confounding, and we did not take aspects such as the use of biological therapy, antibiotics, premature birth, or cesarean section into account; we acknowledge that these aspects could have an impact.[49-51]

Early onset IBD is associated with an increased risk of having a diagnosis of psoriatic arthritis and spondyloarthritis within 10 years after the IBD diagnosis when compared with the matched reference cohort. The difference in the risk of the manifestations between ulcerative colitis and Crohn's disease indicates a difference in pathogenesis between the 2 entities.

Author Contributions

All authors made a significant contribution to the work reported, including the conceptualization and design of the study and interpretation of data. K.L., B.M.N., and L.R.J. applied for funding. F.D.Z., K.L., M.W., B.M.N., and L.R.J. collected and analyzed the data. L.R.J. drafted the manuscript, which was reviewed and revised for intellectual content by all authors. The final article was approved by all authors.

Funding

This work was supported by The Beckett Foundation, The Louis-Hansen Foundation, and Odense University Hospital.

Conflicts of Interest

The authors declare no conflict of interest regarding this work.

Data Availability

The study was approved by the Danish Data Protection Agency (j.no. 20/33781). According to Danish legislation, our approval is to use these register data for the current study only, and it does not allow us to make patient data available to other parties. Other interested researchers may apply for access to data through the Danish Health Data Authority (Sundhedsdatastyrelsen). Ethical review board approval or individual patient consent is not required for register-based studies in Denmark.

References

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet*. 2017;389(10080):1756-1770.
2. Uhlig HH, Schwerd T, Koletzko S, et al.; COLORS in IBD Study Group and NEOPICS. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology*. 2014;147(5):990-1007.e3.
3. Everhov AH, Halfvarson J, Myrelid P, et al. Incidence and treatment of patients diagnosed with inflammatory bowel diseases at 60 years or older in Sweden. *Gastroenterology*. 2018;154(3):518-528.e15.
4. Ghione S, Sarter H, Fumery M, et al.; Epimad Group. Dramatic increase in incidence of ulcerative colitis and Crohn's disease (1988-2011): a population-based study of French adolescents. *Am J Gastroenterol*. 2018;113(2):265-272.
5. Larsen MD, Baldal ME, Nielsen RG, et al. The incidence of Crohn's disease and ulcerative colitis since 1995 in Danish children and adolescents <17 years–based on nationwide registry data. *Scand J Gastroenterol*. 2016;51(9):1100-1105.
6. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol*. 2017;112(7):1120-1134.
7. Nordenvall C, Rosvall O, Bottai M, et al. Surgical treatment in childhood-onset inflammatory bowel disease-a nationwide register-based study of 4695 incident patients in Sweden 2002-2014. *J Crohns Colitis*. 2018;12(2):157-166.
8. Agrawal M, Christensen HS, Bøgsted M, et al. The rising burden of inflammatory bowel disease in Denmark over two decades: a nationwide cohort study. *Gastroenterology*. 2022;163(6):1547-1554.e5.
9. Malmborg P, Grahnquist L, Idestrom M, et al. Presentation and progression of childhood-onset inflammatory bowel disease in Northern Stockholm County. *Inflamm Bowel Dis*. 2015;21(5):1098-1108.
10. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol*. 2009;104(8):2080-2088.
11. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology*. 2008;135(4):1114-1122.
12. Malham M, Jakobsen C, Vester-Andersen MK, et al. Paediatric onset inflammatory bowel disease is a distinct and aggressive phenotype—a comparative population-based study. *GastroHep*. 2019;1(6):266-273.
13. Ludvigsson JF, Busch K, Olen O, et al. Prevalence of paediatric inflammatory bowel disease in Sweden: a nationwide population-based register study. *BMC Gastroenterol*. 2017;17(1):23.
14. Olen O, Askling J, Sachs MC, et al. Increased mortality of patients with childhood-onset inflammatory bowel diseases, compared with the general population. *Gastroenterology*. 2019;156(3):614-622.
15. Lees CW, Barrett JC, Parkes M, Satsangi J. New IBD genetics: common pathways with other diseases. *Gut*. 2011;60(12):1739-1753.
16. Halling ML, Kjeldsen J, Knudsen T, Nielsen J, Hansen LK. Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases. *World J Gastroenterol*. 2017;23(33):6137-6146.
17. Fu Y, Lee CH, Chi CC. Association of psoriasis with inflammatory bowel disease: a systematic review and meta-analysis. *JAMA Dermatol*. 2018;154(12):1417-1423.
18. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. *Gastroenterology*. 2021;161(4):1118-1132.
19. Malik TF, Aurelio DM. *Extraintestinal Manifestations of Inflammatory Bowel Disease*. StatPearls, 2023.
20. Conway G, Velonias G, Andrews E, et al. The impact of co-existing immune-mediated diseases on phenotype and outcomes in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2017;45(6):814-823.
21. Gurung M, Li Z, You H, et al. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*. 2020;51:102590.
22. de Candia P, Prattichizzo F, Garavelli S, et al. Type 2 diabetes: how much of an autoimmune disease? *Front Endocrinol*. 2019;10:451.
23. World Health Organization. *Adolescent Health*. Vol. 2023: World Health Organization, 2023.
24. Mouratidou N, Malmborg P, Jaras J, et al.; SWIBREG Study Group. Identification of childhood-onset inflammatory bowel disease in Swedish healthcare registers: a validation study. *Clin Epidemiol*. 2022;14:591-600.
25. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*. 2010;25(1):1-21.
26. Peter Cummings BM. Analysis of matched cohort data. *Stata J*. 2004;4(3):274-281.
27. Jess T, Jensen BW, Andersson M, Villumsen M, Allin KH. Inflammatory bowel diseases increase risk of type 2 diabetes in a Nationwide Cohort Study. *Clin Gastroenterol Hepatol*. 2020;18(4):881-888.e1.
28. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology*. 2005;129(3):827-836.
29. Charlton R, Green A, Shaddick G, et al.; PROMPT study group. Risk of uveitis and inflammatory bowel disease in people with psoriatic arthritis: a population-based cohort study. *Ann Rheum Dis*. 2018;77(2):277-280.
30. Fragoulis GE, Liava C, Daoussis D, et al. Inflammatory bowel diseases and spondyloarthropathies: from pathogenesis to treatment. *World J Gastroenterol*. 2019;25(18):2162-2176.
31. Chen Y, Chen L, Xing C, et al. The risk of rheumatoid arthritis among patients with inflammatory bowel disease: a systematic review and meta-analysis. *BMC Gastroenterol*. 2020;20(1):192.
32. Pinto-Sanchez MI, Seiler CL, Santesso N, et al. Association between inflammatory bowel diseases and celiac disease: a systematic review and meta-analysis. *Gastroenterology*. 2020;159(3):884-903.e31.
33. Shah A, Walker M, Burger D, et al. Link between celiac disease and inflammatory bowel disease. *J Clin Gastroenterol*. 2019;53(7):514-522.
34. Jolving LR, Nielsen J, Beck-Nielsen SS, et al. The association between maternal chronic inflammatory bowel disease and long-term health outcomes in children—a nationwide cohort study. *Inflamm Bowel Dis*. 2017;23(8):1440-1446.
35. Turpin W, Goethel A, Bedrani L, Croitoru Mdcm K. Determinants of IBD heritability: genes, bugs, and more. *Inflamm Bowel Dis*. 2018;24(6):1133-1148.
36. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490.
37. Nielsen GL, Sorensen HT, Pedersen AB, Sabroe S. Analyses of data quality in registries concerning diabetes mellitus--a comparison between a population based hospital discharge and an insulin prescription registry. *J Med Syst*. 1996;20(1):1-10.
38. Pedersen M, Klarlund M, Jacobsen S, Svendsen AJ, Frisch M. Validity of rheumatoid arthritis diagnoses in the Danish National Patient Registry. *Eur J Epidemiol*. 2004;19(12):1097-1103.
39. Dydensborg S, Toftedal P, Biaggi M, et al. Increasing prevalence of coeliac disease in Denmark: a linkage study combining national registries. *Acta Paediatr*. 2012;101(2):179-184.
40. Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. *Thyroid*. 2002;12(5):411-419.

41. Pedersen OB, Svendsen AJ, Ejstrup L, et al. Ankylosing spondylitis in Danish and Norwegian twins: occurrence and the relative importance of genetic vs. environmental effectors in disease causation. *Scand J Rheumatol.* 2008;37(2):120-126.
42. Karmiris K, Avgerinos A, Tavernaraki A, et al. Prevalence and characteristics of extra-intestinal manifestations in a large cohort of Greek patients with inflammatory bowel disease. *J Crohns Colitis*. 2016;10(4):429-436.
43. Argollo M, Gilardi D, Peyrin-Biroulet C, et al. Comorbidities in inflammatory bowel disease: a call for action. *Lancet Gastroenterol Hepatol*. 2019;4(8):643-654.
44. Ott C, Scholmerich J. Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol*. 2013;10(10):585-595.
45. Harbord M, Annese V, Vavricka SR, et al.; European Crohn's and Colitis Organisation. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis*. 2016;10(3):239-254.
46. Jang HJ, Kang B, Choe BH. The difference in extraintestinal manifestations of inflammatory bowel disease for children and adults. *Transl Pediatr*. 2019;8(1):4-15.
47. Jansson S, Malham M, Paerregaard A, Jakobsen C, Wewer V. Extraintestinal manifestations are associated with disease severity in pediatric onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2020;71(1):40-45.
48. Duricova D, Sarter H, Savoye G, et al.; Epimad Group. Impact of extra-intestinal manifestations at diagnosis on disease outcome in pediatric- and elderly-onset Crohn's disease: a French population-based study. *Inflamm Bowel Dis*. 2019;25(2):394-402.
49. Spangmose AL, Jorgensen MH, Jakobsen C, et al. Pre- and perinatal exposures associated with developing pediatric-onset immune-mediated inflammatory disease: a Danish nation-wide cohort study. *J Autoimmun*. 2023;136:103032.
50. Raisanen L, Viljakainen H, Sarkkola C, Kolho KL. Perinatal risk factors for pediatric onset type 1 diabetes, autoimmune thyroiditis, juvenile idiopathic arthritis, and inflammatory bowel diseases. *Eur J Pediatr.* 2021;180(7):2115-2123.
51. Lund K, Larsen MD, Knudsen T, et al. Infliximab, immunomodulators and treatment failures in paediatric and adolescent patients with Crohn's disease: a nationwide cohort study. *J Crohns Colitis*. 2021;15(4):575-582.