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Parental Inflammatory Bowel Disease and Risk of Asthma in Offspring: A Nationwide Cohort Study in Denmark

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OBJECTIVES: Common genetic and environmental risk factors may explain the concurrent increase in the incidence of both inflammatory bowel disease (IBD) and asthma. We examined whether IBD in a parent is associated with an increased asthma risk in offspring.

METHODS: This was a registry-based cohort study of all children born alive in Denmark in 1979–2009, followed through 2010. IBD and asthma were identified using hospital diagnoses; antiasthma medication was also used to identify asthma. We computed risk of asthma and estimated adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (CIs) using Cox proportional-hazards regression. We evaluated asthma risk according to maternal and paternal IBD, Crohn's disease (CD), and ulcerative colitis (UC). Children without parental IBD were the comparison cohort for all comparisons.

RESULTS: We identified 1,845,281 children, of whom 14,952 (0.8%) had a parent with IBD. The 10-year risk of asthma was 6.9% among offspring of parents with CD, 5.6% among offspring of parents with UC, and 5.0% among offspring of parents without IBD. The aIRR for asthma associated with parental IBD was 0.98 (95% CI: 0.91–1.04). The aIRR was 1.09 (95% CI: 0.98–1.22) for parental CD and 0.92 (95% CI: 0.84–1.00) for parental UC. Results were similar regardless of parent of origin or inclusion of antiasthma medication to define asthma.

CONCLUSIONS: Our data do not provide evidence for an increased risk of asthma in offspring with a parental history of IBD.

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INTRODUCTION

There have been concurrent increases in the occurrence of both inflammatory bowel disease (IBD) and asthma.[1–4] IBD is a collective term used for two diseases, Crohn's disease (CD) and ulcerative colitis (UC). During the first decade of the 2000s, in Europe, the population prevalence was up to 0.5% for UC and up to 0.3% for CD,[3] whereas asthma has become a leading chronic disease in industrialized countries, with prevalence in children reaching up to 20%.[1,2] The two conditions share genetic susceptibility loci,[5] and their concomitantly increasing incidence suggests common environmental risk factors.

Potential environmental risk factors implicated in the development of IBD and asthma include exposures to antibiotics[6,7] and endocrine-disrupting chemicals, which have immunomodulatory properties.[8] Active and passive cigarette smoking[9,10] also increase the risk of both CD and asthma.

IBD and asthma are immune-mediated diseases and can co-occur in the same individual.[11–14] A recent study based on inpatient hospital admissions reported a slightly increased risk of asthma among children with parental CD and UC.[15] However, to our knowledge, this is the only study to have addressed this potential parent/offspring association.

We therefore examined the association between IBD in parents and the risk of asthma in offspring in a cohort study in Denmark. We used prospectively registered data on all types of hospital contacts and on medication use to define study variables.

METHODS

For this cohort study, we linked individual-level data of children and their parents from different population health registries in Denmark. The linkage was possible due to the personal registration number (CPR number), which is a 10-digit unique identifier assigned at birth or immigration and used in all public records. The CPR number has been assigned since 1968 by the Civil Registration System, which uses the number to track residence and vital status.[16]

Study population. The study cohort included all children born alive in Denmark from 1 January 1979 to 31 December 2009 as recorded in the Danish Medical Birth Registry (DMBR). The DMBR has recorded all births in Denmark since 1973, including CPR numbers of the newborn, the mother, and, since 1991, the father.[17] Thus, we used the Civil Registration System to identify fathers of children born before 1991 and the DMBR thereafter. To ensure a minimum of 2-year availability of data on parental medical history (recorded since 1977), we started the cohort assembly from 1979 and excluded children whose parents had not been residents of Denmark for at least 2 years before the child's birth or whose parents had no valid CPR number.

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Data on IBD. From the Danish National Registry of Patients (DNRP),[18] we collected information on paternal IBD before the relevant pregnancy and on maternal IBD before or during the relevant pregnancy. IBD was defined as an inpatient, outpatient, or emergency-room diagnosis of CD or UC. If both CD and UC diagnoses were present for the same parent, the most recently recorded diagnosis was used to classify parental disease. To measure maternal disease activity during pregnancy, we counted the number of IBD admissions recorded from the estimated date of conception and until (and excluding) the date of delivery. To avoid misclassifying planned follow-up visits as disease flare-ups, we required that IBD-related hospital stays lasting $\geq$2 days to be considered indicative of the disease activity. The DNRP records all inpatient hospitalizations at nonpsychiatric public hospitals in Denmark since 1977 and emergency and outpatient contacts since 1995. Diagnoses have been coded using the eighth revision of the International Classification of Diseases (ICD-8) until the end of 1993 and the tenth revision (ICD-10) thereafter. Positive predictive values of DNRP-recorded diagnoses are 97% for CD and 90% for UC.[19]

Data on asthma. Asthma in children was defined as an inpatient, outpatient, or emergency-room asthma diagnosis recorded in the DNRP.[18] The positive predictive values of DNRP-recorded asthma diagnoses in children aged 6–14 years are 85%.[20]

Furthermore, in a restricted population of children born from 1996 onwards, we added to the asthma definition an algorithm based on filled prescriptions for both inhaled β-agonists and inhaled glucocorticoids. In the United States, in patients aged 5–45 years, the algorithm based on at least one prescription of an inhaled β-agonist and an inhaled glucocorticoid has a positive predictive value of 100% for identifying ''any asthma'' (definitive asthma, wheezing, chronic obstructive pulmonary disease, or allergy), and a positive predictive value of 80% for ''definitive asthma.''[21] In the Danish setting, antiasthma prescriptions have also been found useful in identifying asthma in children (6–14 years of age).[22]

We used the Danish Registry of Medicinal Product Statistics (RMPS) to identify prescriptions. The RMPS records all prescriptions filled at Danish outpatient pharmacies, including patient CPR numbers, Anatomical Therapeutic Chemical code, amount dispensed, and date of sale. The RMPS is complete from 1995 onward.[23] To reduce potential misclassification of children with wheezing as asthmatics, we required that a given medication regimen be dispensed twice in order for a child to be counted as having asthma. Date of asthma onset in the restricted population was the date of the first hospital inpatient or outpatient diagnosis or fulfilled prescription algorithm, whichever was earlier.[21]

Data on covariates. From the available data sources, we identified information on known risk factors for asthma.[7,24–27] From the DMBR, we obtained data on sex of child, birth order, multiple birth, gestational age, mother's age at delivery, mode of delivery, maternal smoking during pregnancy (recorded from 1991), and maternal pregravid body mass index (recorded from 2004). From the RMPS, we obtained data on maternal use of antibiotics during pregnancy, and from the DNRP, data on parental asthma, defined on the basis of hospital diagnoses. The algorithms used to define study variables are provided in the Appendix.

Statistical analyses. We excluded 66 children with IBD in both parents (including four children with asthma) as this group was too small to allow a meaningful interpretation.

In our study cohort, the follow-up started on the day of birth and ended on the date of asthma onset, emigration, death, or 31 December 2010, whichever came first. First, we examined distributions of perinatal characteristics at birth according to parental IBD status. Second, we estimated 2-year and 10-year risk of asthma according to parental IBD status, with death as a competing risk.[28] Third, using Cox proportional-hazards regression, we computed crude and adjusted hazard ratios as estimates of crude and adjusted incidence rate ratios (IRRs and aIRRs) with 95% confidence intervals (CIs) for asthma. We used the following categories of IBD: parental IBD, maternal IBD only, paternal IBD only, parental CD, maternal CD only, paternal CD only, parental UC, maternal UC only, and paternal UC only. Children without a record of IBD in mother or father served as the comparison cohort for all comparisons. The IRRs were adjusted for year of birth, child's sex, mode of delivery, mother's age at delivery, birth order, multiple birth, and parental asthma. The assumption of proportional hazards was assessed graphically and found valid. To assess whether the risk of asthma varied by maternal disease activity during pregnancy, we estimated IRRs and aIRRs in categories defined by the number of mother's CD- and UC-related hospital admissions during the relevant pregnancy (0, 1, and $\geq$2). This analysis was done in the entire cohort and separately among children born at term (week 37 or later) to remove potential effect of prematurity on early-life respiratory complications.

We conducted analyses to address differences in recording practices over time. We stratified by calendar period of availability of outpatient diagnoses in the DNRP (before 1995/1995 onwards). We also conducted an analysis restricting to children born in 1996 or later, including the antiasthma medication in the definition of asthma and also adjusting for maternal smoking and use of antibiotics during pregnancy. In addition, we restricted the latter analysis to the subset of children born in 2004 onwards to adjust for maternal pregravid body mass index. Finally, as a definitive diagnosis of asthma cannot be made until a child is at least 5 years old,[29] we repeated the analyses whereby follow-up for each child started at age 5 years. This analysis was done both for the entire cohort and for children born in 1996 or late, to allow inclusion of antiasthma medication in the asthma definition. We used Stata software version 12 to analyze the data (StataCorp LP, College Station, TX). The study was approved by the Danish Data Protection Agency (record no. 2013-41-1790).

RESULTS

Descriptive data. We identified 1,845,281 children born between 1979 and 2009 (51.3% boys) of whom 14,952 (0.8%) had a parent with IBD. Children born to parents with CD or UC were more likely than children of parents without

IBD to have had older mothers, to be born preterm or by caesarean delivery, and to have a parent with asthma. Maternal smoking or use of antibiotics during pregnancy and low pregravid body mass index were more prevalent among children with parental CD than among children with parental UC or no parental IBD (Table 1).

During follow-up 106,939 children were diagnosed with asthma of whom 856 had a parent with IBD. The median follow-time was 14.9 years (quartiles: 7.3–22.7). Median age at asthma onset was 1.6 years (quartiles: 0.9–4.4) for children with parental CD, 1.9 years (quartiles: 1.0–5.1) for children with parental UC, and 3.2 years (quartiles: 1.2–8.5) for children without parental IBD. Corresponding observed values when starting follow-up at age 5 years were 8.0 years (quartiles: 5.8–11.2), 8.7 years (quartiles: 6.7–11.6), and 9.5 years (quartiles: 6.7–14.2), respectively.

Risk of asthma. Among children with parental CD, the 2-year risk of asthma was 3.7% and the 10-year risk was 6.9%. Among children with parental UC, the respective risks were 2.8 and 5.6%. Among children without parental IBD, the 2- and 10-year risks were 2.3 and 5.0%.

Incidence rate ratios. Overall, the aIRR for asthma associated with parental IBD was 0.98 (95% CI: 0.91–1.04). For parental CD, the aIRR was 1.09 (95% CI: 0.98–1.22), and for parental UC, the aIRR was 0.92 (95% CI: 0.84–1.00). Results did not change when maternal and paternal CD and UC were examined separately (Table 2) or stratified by calendar period (results not shown). Risk of asthma was elevated among children born to mothers with two or more CD admissions during pregnancy (aIRR 1.74; 95% CI: 1.03–2.94; Table 3). This aIRR decreased to 1.42 (95% CI: 0.76–2.64) after restricting this analysis to children born in gestational week 37 or later (results not shown). There was no association between UC-related admissions during pregnancy and asthma (Table 3). Adding antiasthma medication to the definition of asthma (for children born in 1996–2009, $N = 871{,}674$) obtained aIRR for parental IBD of 1.05 (95% CI: 0.97–1.14), for parental CD of 1.11 (95% CI: 0.98–1.25), and for parental UC of 1.01 (95% CI: 0.92–1.12). The estimates did not vary by parent of CD/UC origin (results not shown).

The estimates for parental CD and parental UC remained unaffected by starting follow-up at age 5 years in the full cohort (estimates not shown); however, the association between two or more maternal CD-related admissions during pregnancy and asthma was no longer present (Table 3). When restricting the analyses with follow-up starting at age 5 years to children born in 1996 or later, no association was observed for either parental UC or CD (results not shown).

Additional adjustment in subcohorts with available data for pregravid body mass index did not affect the estimates (data not shown). All estimates are available from the authors upon request.

DISCUSSION

In this nationwide population-based cohort study of nearly 2 million individuals, we found no evidence for an overall association between parental IBD and asthma in offspring. This finding did not vary by calendar period and was unaffected by choice of asthma-defining algorithms.

The strengths of this study are its large size and setting in a universal healthcare system, allowing long and complete follow-up based on routinely recorded health-related events. The validity of the registries used in this study is high,[23,30] including quality of IBD diagnostic coding in the DNRP.[19] Furthermore, data on IBD and asthma were collected prospectively and independently of each other. Independent and routine data collections reduce the risk of recall, selection, and diagnostic biases. Available data sources allow for adjustment for confounding by parental asthma and maternal smoking during pregnancy. Furthermore, we can 100% identify persons who claim being the father and assume that rate of nonbiological paternity is random across the status of asthma and IBD.[16] If there were an association between parental IBD and asthma in offspring, nondifferential error in classifying IBD or asthma status could dilute the estimates of association to create an apparent null effect. For example, our asthma algorithm and databases could mistakenly capture some small children with wheezing and no asthma. However, this seems unlikely given that similar null results were observed when starting follow-up at age 5 years.

Taken together, the epidemiologic studies of IBD and asthma in the same individual suggested the presence of an association,[11–14] and this evidence provided the rationale for this study. Sibtain *et al.*[31] reported a 53% prevalence of a family history of asthma among children with IBD in a hospital-based cross-sectional study. To the best of our knowledge, the association between parental IBD and asthma in offspring was addressed in one epidemiologic study. Using the cohort design, Hemminki *et al.*[15] examined familial risks of 32 different immune-related diseases among 441,642 individuals with these diseases based on inpatient hospital diagnoses in Sweden. The standardized IRRs were 1.1 (95% CI: 1.0–1.2) for asthma among offspring of a parent with CD and 1.2 (95% CI: 1.1–1.3) for asthma among offspring of a parent with UC. Estimates for maternal and paternal IBD were not reported. Hemminki *et al.*[15] studied multiple outcomes and did not include outpatient asthma diagnoses or medications in asthma algorithms.

Similar to the Swedish study, we observed a weak association of parental CD with asthma in some analyses. Hemminki *et al.*[15] could not adjust for smoking, and as we were only able to adjust for maternal smoking during pregnancy in children born from 1996 onwards, not fully measured confounding by parental smoking could explain some of the weak association observed in our study.

In the light of the overall null findings, the explanation for an observed increased risk of asthma in the subgroup of children with two or more maternal CD-related admissions during pregnancy is probably noncausal. Possible explanations are chance or upward detection bias of asthma among young children with asthma-like symptoms and more frequent contact with health care because of maternal CD. Furthermore, restriction of the analyses to children born at term reduced the association for maternal CD-related admissions, suggesting that the association may be attributable to maternal pregnancy complications, rather than IBD, causing respiratory symptoms in small children.[32]

Table 1 Characteristics of children born in Denmark during 1979–2009 according to parental type of inflammatory bowel disease (IBD), $N = 1{,}845{,}281$

Characteristics	Parental IBD		No parental IBD ($n = 1{,}830{,}329$) *n* (%)
	Parental Crohn's disease ($n = 5{,}106$) *n* (%)	Parental ulcerative colitis ($n = 9{,}846$) *n* (%)	
Parental IBD			
Maternal	3,102 (60.8)	5,473 (55.6)	—
Paternal	2,004 (39.2)	4,373 (44.4)	—
Sex of child			
Female	2,478 (48.5)	4,816 (48.9)	890,959 (48.7)
Male	2,628 (51.5)	5,030 (51.1)	939,370 (51.3)
Year of birth			
1979–1984	170 (3.3)	551 (5.6)	314,398 (17.2)
1985–1989	251 (4.9)	787 (8.0)	272,798 (14.9)
1990–1994	522 (10.2)	1,195 (12.1)	316,007 (17.3)
1995–1999	936 (18.3)	1,752 (17.8)	318,426 (17.4)
2000–2004	1,393 (27.3)	2,537 (25.8)	306,827 (16.7)
2005–2009	1,834 (35.9)	3,024 (30.7)	301,873 (16.5)
Mother's age at delivery (years)			
<25	626 (12.3)	973 (9.9)	371,149 (20.3)
25–34	3,885 (76.1)	7,585 (77.0)	1,296,539 (70.8)
≥ 35	595 (11.7)	1,288 (13.1)	162,641 (8.9)
Gestational age (weeks)			
<37	416 (8.3)	754 (7.7)	103,264 (5.6)
37–41	4,387 (85.9)	8,334 (84.6)	1,538,939 (84.1)
≥ 42	279 (5.5)	674 (6.5)	145,334 (8.0)
Missing	24 (0.5)	84 (0.9)	42,792 (2.3)
Mode of delivery			
Vaginal	3,776 (74.0)	7,618 (77.4)	1,548,727 (84.6)
Cesarean	1,330 (26.1)	2,228 (22.6)	281,602 (15.4)
Birth order[a]			
1	2,374 (46.5)	4,115 (41.8)	827,582 (45.2)
≥ 2	2,732 (53.5)	5,731 (58.2)	1,002,747 (54.8)
Maternal asthma			
No	4,963 (97.2)	9,651 (98.0)	1,806,905 (98.7)
Yes	143 (2.8)	195 (2.0)	23,424 (1.3)
Paternal asthma			
No	4,999 (98.0)	9,667 (98.2)	1,812,499 (99.0)
Yes	107 (2.0)	179 (1.8)	17,830 (1.0)
Multiple birth			
No	4,923 (96.4)	9,487 (96.4)	1,770,491 (96.7)
Yes	183 (3.6)	359 (3.7)	59,838 (3.3)
Prenatal exposure to antibiotics[b]	($n = 4{,}001$)	($n = 7{,}018$)	($n = 860{,}655$)
No	2,527 (63.2)	4,692 (66.9)	586,742 (68.2)
Yes	1,474 (36.8)	2,326 (33.1)	273,913 (31.8)
Maternal smoking during pregnancy[b]			
No	2,974 (74.3)	5,860 (83.5)	665,964 (77.4)
≤ 10 cigarettes/day	640 (16.0)	703 (10.0)	122,659 (14.3)
>10 cigarettes/day	235 (5.9)	210 (3.0)	40,790 (4.7)
Missing	152 (3.8)	245 (3.5)	31,242 (3.6)
Maternal pregravid body mass index[c]	($N = 2{,}185$)	($N = 3{,}586$)	($N = 363{,}381$)
<18.5	127 (5.8)	184 (5.1)	16,577 (4.6)
18.5–24	1,269 (58.1)	2,116 (59.0)	209,956 (57.8)
25–29	424 (19.4)	656 (18.3)	71,261 (19.6)
≥ 30	220 (10.1)	388 (10.8)	39,881 (11.0)
Missing	145 (6.6)	242 (6.8)	25,706 (7.1)

[a]Children of multiple births are coded in same birth order.
[b]Children born from 1996 onwards, $N = 871{,}674$.
[c]Children born from 2004 onwards, $N = 369{,}152$.

Table 2 Incidence rates and crude and adjusted incidence rate ratios for asthma in Danish children born during 1979–2009 according to parental IBD status (*N* = 1,845,281)

	N	Children with asthma, *n* (%)	IR (per 1,000 PY)	Crude IRR (95% CI)	aIRR[a] (95% CI)
Parental IBD					
No parental IBD	1,830,329	106,083 (5.8)	3.8	1.00 (Ref.)	1.00 (Ref.)
Parental IBD	14,952	856 (5.7)	5.6	1.20 (1.12–1.28)	0.98 (0.91–1.04)
Maternal IBD	8,575	492 (5.7)	5.4	1.19 (1.09–1.30)	0.97 (0.89–1.06)
Paternal IBD	6,377	364 (5.7)	5.8	1.22 (1.10–1.35)	0.99 (0.89–1.09)
Parental CD	5,106	328 (6.4)	6.9	1.41 (1.27–1.57)	1.09 (0.98–1.22)
Maternal CD	3,102	203 (6.5)	6.9	1.43 (1.25–1.64)	1.10 (0.95–1.26)
Paternal CD	2,004	125 (6.3)	6.8	1.38 (1.16–1.65)	1.09 (0.91–1.29)
Parental UC	9,846	528 (5.4)	5.0	1.10 (1.01–1.20)	0.92 (0.84–1.00)
Maternal UC	5,473	289 (5.2)	4.7	1.06 (0.94–1.19)	0.89 (0.80–1.00)
Paternal UC	4,373	239 (5.5)	5.4	1.15 (1.01–1.30)	0.94 (0.83–1.07)

aIRR, adjusted incidence rate ratio; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IR, incidence rate; IRR, incidence rate ratio; PY, person-years; Ref., reference; UC, ulcerative colitis.
[a]Adjustment: sex of child, year of birth, mother's age at delivery, mode of delivery, multiple birth, birth order, asthma in mother, and asthma in father.

Table 3 Risk of asthma in Danish children born during 1979–2009 according to the number of maternal IBD-related admissions during pregnancy

Maternal IBD admissions during pregnancy	*N*	Children with asthma, *n* (%)	Crude IRR (95% CI)	aIRR[a] (95% CI)
*All children (*N = *1,845,281)*				
No maternal IBD	1,836,706	106,447 (5.8)	1.00 (Ref.)	1.00 (Ref.)
Maternal CD				
No admissions	1,729	107 (6.2)	1.30 (1.08–1.57)	1.05 (0.87–1.27)
1 admission	1,235	82 (6.6)	1.54 (1.24–1.91)	1.08 (0.87–1.35)
≥2 admissions	138	14 (10.1)	2.15 (1.27–3.63)	1.74 (1.03–2.94)
Maternal UC				
No admissions	3,229	178 (5.5)	1.05 (0.91–1.22)	0.94 (0.81–1.09)
1 admission	2,015	97 (4.8)	1.06 (0.87–1.24)	0.80 (0.66–0.98)
≥2 admissions	229	14 (6.1)	1.18 (0.70–2.00)	1.04 (0.61–1.75)
*Children at age ≥5 years (*N = *1,581,040)*				
No maternal IBD	1,574,750	50,816 (3.2)	1.00 (Ref.)	1.00 (Ref.)
Maternal CD				
No admissions	1,226	34 (2.8)	1.11 (0.80–1.56)	1.07 (0.76–1.50)
1 admission	834	26 (3.1)	1.57 (1.07–2.30)	1.48 (1.00–2.17)
≥2 admissions	101	3 (3.0)	1.14 (0.37–3.55)	1.08 (0.35–3.34)
Maternal UC				
No admissions	2,514	71 (2.8)	0.99 (0.78–1.25)	0.95 (0.76–1.20)
1 admission	1,444	22 (1.5)	0.72 (0.47–1.09)	0.71 (0.46–1.07)
≥2 admissions	171	6 (3.5)	1.18 (0.53–2.63)	1.16 (0.52–2.59)

aIRR, adjusted incidence rate ratio; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IRR, incidence rate ratio; Ref., reference; UC, ulcerative colitis.
[a]Adjustment: sex of child, year of birth, mother's age at delivery, mode of delivery multiple birth, birth order, asthma in mother, and asthma in father.

Although IBD and asthma may be associated in individuals, the overall findings of our study reassuringly suggest that IBD in a parent does not increase the risk of asthma in offspring.

CONFLICT OF INTEREST

Guarantor of the article: Ane Birgitte Telén Andersen, MPH.
Specific author contributions: study concept and design, analyses, interpretation of data, manuscript writing, manuscript revision, editing, and decision to publish: Ane Birgitte Telén Andersen; study concept and design, supervising in analyses, interpretation of data, revision of manuscript, editing, and decision to publish: Vera Ehrenstein, Rune Erichsen, and Henrik Toft Sørensen; study concept and design, participated in data analysis, interpretation of data, revision of manuscript, editing, and decision to publish: Trine Frøslev. All authors had full access to all data.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

Inflammatory bowel disease (IBD) and asthma may co-occur in the same individual.

The association between parental IBD and asthma in the offspring is poorly documented.

WHAT IS NEW HERE

Of the 1,845,281 children born between 1979 and 2009 in Denmark, 14,952 (0.8%) had a parent with IBD.

Our study provides no evidence of an association between parental IBD and asthma in the offspring.

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APPENDIX 1

ATC-codes for included medications

Drug	ATC-code
β-agonist	R03AC
Inhaled glucocorticoids	R03BA
Systemic antibiotics	J01

ICD-8 and ICD-10 codes for IBD and asthma

Diagnoses	ICD classification
Crohns Disease	ICD-8: 563.01 ICD-10:K50
Ulcerative Colitis	ICD-8:563.19, 569.04 ICD-10: K51
Asthma	ICD-8: 493 ICD-10: J45, J46