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Paternal use of medications for inflammatory bowel disease and the risk of hospital-diagnosed infections in the offspring: a nationwide cohort study

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Summary

Background: Information regarding the impact of paternal inflammatory bowel disease (IBD) medications on child outcomes is scarce.

Aim: To examine the risk of childhood infections associated with fathers' use of anti-inflammatory/immunosuppressive medications taken before conception.

Methods: This is a nationwide cohort study based on Danish health registries, comprising all live-born singleton children born between January 1997 and February 2019 who were fathered by men with IBD. Exposed cohorts included children fathered by men treated with 5-aminosalicylates (5-ASAs), thiopurines, corticosteroids or anti-tumour necrosis factor-α (anti-TNF-α) agents within 3 months before conception. The unexposed cohort included children not exposed to paternal IBD medications. Outcomes were the first infection, diagnosed in the hospital setting in the first year of life, and from the age of 1 to 3 years.

Results: In all, 2178 children were fathered by men exposed to 5-ASAs, 843 to thiopurines, 417 to systemic corticosteroids and 436 to anti-TNF-α agents; 6799 children were unexposed. The adjusted hazard ratio (aHR) for infections within the first year of life for 5-ASAs was 0.78 (95% CI, 0.66–0.91), thiopurines 0.89 (95% CI, 0.73–1.09), systemic corticosteroids 0.95 (95% CI, 0.70–1.29), and anti-TNF-α agents 1.17 (95% CI, 0.94–1.46). The aHR for infections from 1 to 3 years for 5-ASAs was 0.97 (95% CI, 0.83–1.13), thiopurines 0.87 (95% CI, 0.71–1.07), systemic corticosteroids 1.25 (95% CI, 0.94–1.65), and anti-TNF-α agents 0.79 (95% CI, 0.60–1.03).

Conclusion: Fathers' use of anti-inflammatory/immunosuppressive medications before conception was not significantly associated with childhood infections. These results fill an important research gap regarding paternal medication safety.

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1 | INTRODUCTION

Men and women with inflammatory bowel disease (IBD) are commonly diagnosed at a time in their lives when they are considering having children. While there is increasing knowledge of the effect of maternal immunosuppressive medications taken during pregnancy and child outcomes, there is a lack of data on the impact of paternal medications on child health outcomes.[1,2] The question of how future fathers with autoimmune diseases should be treated to improve (or at least not impair) their chances of achieving a successful pregnancy and a healthy offspring remains a challenge for physicians and researchers.[1–3] Accumulating evidence has demonstrated that preconception paternal factors do affect the offspring.[3–8] Paternal preconception stress, diet and exposure to environmental toxins have been associated with altered hypothalamic–pituitary–adrenal axis function, birth defects, cancers, growth, obesity and cardiometabolic risk factors in the offspring.[7] Furthermore, animal studies have documented that epigenetic modifications encoded in sperm are heritable and influence offspring phenotypes.[7,8] Chemical and environmental exposures may induce oxidative stress that results in mitochondrial or nuclear DNA damage or affect the sperm epigenome by altering DNA methyltransferase or histone deacetylase activity and thus interfering with hormonal regulation or sperm development.[2–4,8] Thus, preconception toxigenic exposures could increase the risk of offspring disease by epigenetic modifications in the germline, and expectant fathers' use of disease-modifying medication before conception should be considered from this perspective. Based on these arguments, there is a great demand for studies to determine the response of sperm epigenetics in relation to early life environmental exposures.[3]

The lack of studies on preconception paternal exposure to immunosuppressive drugs and the impact on offspring health was confirmed in a recent large systematic review.[6] Only a few previous studies have been published on adverse birth outcomes (preterm birth, small for gestational age and congenital malformations), even fewer studies on long-term outcomes, and no studies on childhood infections.[9–14]

We hypothesise that for men with IBD, preconception exposure to anti-inflammatory/immunosuppressive medications may potentially affect offspring health outcomes. Of special concern is the risk of childhood infections due to paternal use of corticosteroid, thiopurine and anti-TNF-α medications. These medications suppress the immune system in general and may have downstream effects on offspring health. Using the Danish national registries, we performed a nationwide cohort study of men with IBD exposed to thiopurines, systemic corticosteroids, biologics and 5-aminosalicylate medications (5-ASAs) prior to conception to assess the risk of infections in the offspring.

2 | MATERIALS AND METHODS

2.1 | Design and study setting

This is a nationwide cohort study. We used three nationwide Danish health registries: (i) the Danish National Patient Registry (DNPR),[15,16] (ii) the Danish Medical Birth Registry (MBR)[17,18] and (iii) the National Prescription Registry (NPR).[19,20] Furthermore, the Danish Central Personal Registration system provided information on death, immigration and the fatherhood of children born in Denmark.[21,22] Data were linked on an individual level using the unique civil registration number which is assigned to all Danish residents at birth.

The DNPR consists of data from all discharges from the Danish hospitals since 1977 and all outpatients visits since 1994.[15,16] Basic data include information on hospitals, departments, surgeries and procedures performed, diagnoses given at the hospitals, along with date and time of admission and discharge. All diagnostic codes from 1977 to the end of 1993 are coded according to the Danish version of the International Classification of Diseases ICD-8, and since 1994 according to the Danish version of ICD-10.

The MBR contains information on all births in Denmark since 1973, both in hospitals and at home, along with data about the mother, the birth and child, e.g. age of mother at the time of birth and smoking status, birthdate, mode of delivery, weight and length of the child, and gestational age, data on father and information related to pregnancy and birth outcomes.[17,18]

The NPR provides information on all redeemed prescriptions in all pharmacies in Denmark. The information comprises a type of medication, all classified according to the ATC [Anatomical Therapeutic Chemical Classification] system, and place and time of redemption. The Danish NPR contains all out-patient drug prescriptions since 1 January 1995.[19,20] Using the civil registration number, it is possible to obtain the prescription history of each person. We identified users of 5-ASAs, thiopurines (azathioprine and mercaptopurine), systemic corticosteroids and tumour necrosis factor-α (TNF-α) agents.

2.2 | Study population

We included all singleton live-born children born between 1 January 1997 and 1 March 2019 with conception date registered in the MBR with a father who was diagnosed with IBD (ulcerative colitis (UC) or Crohn's disease (CD)) before the child's conception date. Data on diagnoses of IBD were retrieved from the DNPR according to ICD8 (56319 and 56904) and ICD10 (DK51) to identify UC and ICD8 (56301) and ICD10 (DK50) to identify CD for the fathers.

2.3 | Exposed and unexposed cohorts

Children fathered by men with IBD treated with IBD medications prior to conception constituted the exposed cohorts. In the exposed cohorts, we included children from the study population, who were fathered by men who had filled at least one prescription with specific IBD medications within a period of 3 months before the date of conception. We had four sub-groups of exposed children; those who were fathered by men using 5-ASAs, thiopurines, corticosteroids or anti-TNF-α agents. If a child had a father who had filled a prescription for both thiopurines and corticosteroids, for example this child was

presented as exposed in both cohorts. Paternal preconceptual use of medications was retrieved from the national prescription registry. The medications were identified by their Anatomical Therapeutical Chemical Classification (ATC) codes (5-ASA: A07EC, thiopurines: L04AX01 (azathioprine) and L01BB02 (mercaptopurine), systemic corticosteroids: H02AB02 (dexamethasone), H02AB04 (methylprednisolone), H02AB06 (prednisolone), H02AB07 (prednisone) and H02AB09 (hydrocortisone) and the TNF-α group of agents, L04AB). In the DNPR, we also identified procedure codes of thiopurines (BWHB83) and TNF-α agents (BOHJ18A).

The unexposed cohort consisted of all children fathered by men with IBD who had not filled a prescription for IBD medications within 3 months prior to conception.

2.4 | Infection as outcomes

The outcome was defined as the first infection of any kind in the child's first year of life, and the first infection of any kind from the age of 1 to 3 years. Patients with these events were all diagnosed in the Danish hospital system. Infections only diagnosed by the general practitioner are thus not included. The included infections are identified by the ICD10 codes in the DNPR spanning over infections of the respiratory tract and gastrointestinal tract, urological and gynaecological infections, infections of the skin and subcutaneous tissue, sepsis and other infections. A complete list of the ICD10 codes is found in Table S1.

2.5 | Data on possible confounders

The age of mother and father at the time of delivery was found in the Danish Central Personal Registration System. The Body Mass Index (BMI), smoking status of the mother at the start of pregnancy, gestational age and weight of the child were found in the MBR. Gestational age of less than 37 weeks was defined as preterm birth. The combination of weight and gestational age was used to define if the child was small for gestational age (SGA).[23] Information on the Charlson Comorbidity index of the mother and the father was retrieved from the DNPR.[24]

2.6 | Statistics

Contingency tables were constructed for the main study variables according to the four exposed cohorts and the unexposed cohort. The follow-up of the children started on the date of the live birth and ended on the date of the first infection of any kind, emigration, death or third birthday, whichever came first. We estimated the hazard ratio (HR) by a Cox proportional hazard regression to assess whether the exposed and unexposed cohorts had different outcomes. The HR for infections, with 95% confidence intervals (CI), were evaluated in children aged 0–1 year and 1–3 years. According to the four paternal medication exposure groups, we plotted the cumulative proportion of infections for all children from the time of birth to 3 years of age.

For all analyses, we adjusted for the variables mentioned in Table 1 (paternal age at birth, Charlson Comorbidity index of the father, type of IBD of the father, maternal age at birth, maternal Charlson Comorbidity, maternal BMI, maternal smoking status, the child's birth year, sex of the child, SGA and preterm birth). In addition, we mutually adjusted for paternal use of 5-ASAs 3 months before pregnancy until conception, paternal use of thiopurines 3 months before pregnancy until conception, paternal use of systemic corticosteroids 3 months before pregnancy until conception and paternal use of anti-TNF-α agent 3 months before pregnancy until conception.

2.7 | Permissions

The study was approved by the Danish Data Protection Agency (j.nr. 20/4674). This study follows all currently applicable Danish laws regarding scientific research. According to Danish law, no ethical approvals of register-based studies are necessary. The study was non-interventional and did not require direct patient contact.

2.8 | Patient and public involvement

Patient representatives are part of the research council at the Center for Clinical Epidemiology, Odense University Hospital, and patient representatives have been involved in the processes of this study (discussion of the ideas of the study and the outcome assessments). Patient representatives have not been part of the design of the study, analyses of the data or manuscript writing.

3 | RESULTS

In all, 2178 children were fathered by men exposed to 5-ASAs, 843 children by fathers exposed to thiopurines, 417 to systemic corticosteroids, and 436 to anti-TNF-α agents. These 3874 exposed children were fathered by 2385 different men. There was a total of 6799 unexposed children, fathered by 4591 men who did not receive any IBD medications within 3 months prior to conception (Table 1). The father's age was about the same in all groups as was the mother's age at the time of delivery. Most fathers had no comorbid diseases. Children exposed to systemic corticosteroids were more likely to have fathers with comorbid diseases. Children exposed to systemic steroids and anti-TNF-α agents were more likely to have fathers with CD and children exposed to 5-ASA agents were more likely to have fathers with UC. The percentage of SGA was lower in the 5-ASA and unexposed groups and the percentage of preterm infants was lower in the unexposed groups (Table 1).

The aHR for infections within the first year of life in children born to fathers who received 5-ASA medications within 3 months

TABLE 1 Singleton children fathered by men with IBD, with and without exposure to IBD medications within 3 months prior to conception

	Exposed to 5-ASA (*N* = 2178)	Exposed to thiopurines (*N* = 843)	Exposed to systemic corticosteroids (*N* = 417)	Exposed to anti-TNF-α agents (*N* = 436)	Not exposed to IBD medications prior to conception (*N* = 6799)
Age of the father at the time of delivery (years), Median (interquartile range)	33 (30–36)	32 (29–36)	32 (29–35)	32 (28–35)	33 (30–37)
Age of the father at time of delivery in categories (years)					
<30, *N* (%)	484 (22.2)	257 (30.5)	122 (29.3)	150 (34.4)	1635 (24.1)
30–35, *N* (%)	884 (40.6)	311 (36.9)	173 (41.5)	151 (34.6)	2415 (35.5)
≥35, *N* (%)	810 (37.2)	275 (32.6)	122 (29.2)	135 (31.0)	2749 (40.4)
Charlson Comorbidity index of the father					
0, *N* (%)	1925 (88.4)	720 (85.4)	333 (79.9)	363 (82.7)	5821 (85.6)
≥1, *N* (%)	253 (11.6)	123 (14.6)	84 (20.1)	76 (17.4)	978 (14.4)
Type of IBD of the father					
UC, *N* (%)	1864 (85.6)	424 (50.3)	160 (38.4)	168 (38.5)	4468 (65.7)
CD, *N* (%)	314 (14.4)	419 (49.7)	257 (61.6)	268 (61.5)	2331 (34.3)
Age of the mother at the time of delivery (years), Median (interquartile range)	31 (28–34)	30 (27–33)	30 (27–33)	30 (27–33)	31 (28–34)
Age of the mother at time of delivery in categories (years)					
<30, *N* (%)	873 (40.1)	387 (45.9)	200 (48.0)	211 (48.4)	2754 (40.5)
30–35, *N* (%)	854 (39.2)	335 (39.7)	147 (35.2)	154 (35.3)	2551 (37.5)
≥35, *N* (%)	451 (20.7)	121 (14.4)	70 (16.8)	71 (16.3)	1494 (22.0)
BMI of the mother (kg/m^2)					
<18.5, *N* (%)	84 (3.9)	30 (3.6)	11 (2.6)	16 (3.7)	211 (3.1)
18.5–24.9, *N* (%)	1281 (58.8)	608 (72.1)	253 (60.7)	354 (81.2)	4159 (61.2)
≥30, *N* (%)	174 (8.0)	91 (10.8)	32 (7.7)	59 (13.5)	644 (9.5)
Missing, *N* (%)	639 (29.3)	114 (13.5)	121 (29.0)	7 (1.6)	1785 (26.2)
Maternal smoking status					
No, *N* (%)	1905 (87.5)	742 (88.0)	342 (82.1)	387 (88.8)	5586 (82.2)
Yes, *N* (%)	162 (7.4)	82 (9.7)	52 (12.4)	42 (9.6)	865 (12.7)
Missing, *N* (%)	111 (5.1)	19 (2.3)	23 (5.5)	7 (1.6)	348 (5.1)
Charlson Comorbidity of the mother					
0, *N* (%)	2031 (93.3)	776 (92.0)	393 (94.2)	391 (89.7)	6245 (91.8)
≥1, *N* (%)	147 (6.7)	67 (8.0)	24 (5.8)	45 (10.3)	554 (8.2)

TABLE 1 (Continued)

	Exposed to 5-ASA (N = 2178)	Exposed to thiopurines (N = 843)	Exposed to systemic corticosteroids (N = 417)	Exposed to anti-TNF-α agents (N = 436)	Not exposed to IBD medications prior to conception (N = 6799)
Calendar period of child birth					
1997–2000, *N* (%)	318 (14.6)	45 (5.3)	59 (14.2)	0	848 (12.5)
2001–2005, *N* (%)	488 (22.4)	106 (12.6)	88 (21.1)	<5	1362 (20.0)
2006–2010, *N* (%)	500 (23.0)	207 (24.6)	106 (25.4)	57 (13.1)	1579 (23.2)
2011–2015, *N* (%)	513 (23.6)	280 (33.2)	100 (24.0)	177 (40.6)	1678 (24.7)
2016–2019, *N* (%)	359 (16.5)	205 (24.3)	64 (15.3)	299 (45.6)	1332 (19.6)
Sex of child, male, *N* (%)	1141 (52.4)	425 (50.4)	221 (53.0)	211 (48.5)	3485 (51.3)
Small for gestational age					
Yes, *N* (%)	48 (2.2)	22 (2.6)	15 (3.6)	12 (2.8)	153 (2.3)
Missing, *N* (%)	<5		<5		14 (0.2)
Preterm birth, *N* (%)	114 (5.2)	48 (5.7)	22 (5.3)	25 (5.7)	330 (4.9)

Abbreviations: BMI, body mass index; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

of conception was 0.78 (95% CI, 0.66–0.91), thiopurines 0.89 (95% CI, 0.73–1.09), systemic corticosteroids 0.95 (95% CI, 0.70–1.29) and anti-TNF-α agents 1.17 (95% CI, 0.94–1.46) (Table 2).

The aHR for infections from 1 to 3 years of life in children born to fathers who used 5-ASA medications within 3 months of conception was 0.97 (95% CI, 0.83–1.13), thiopurines 0.87 (95% CI, 0.71–1.07), systemic corticosteroids 1.25 (95% CI, 0.94–1.65) and anti-TNF agents 0.79 (95% CI, 0.60–1.03) (Table 2).

Figure 1 cumulative proportion of infections from the time of birth to 3 years of age according to the time of the first infection in the children exposed to IBD medications.

4 | DISCUSSION

We report for the first time the association between fathers with IBD using anti-inflammatory/immunosuppressive medications and the risk of hospital-diagnosed childhood infections. In the first year of life, children whose fathers used 5-ASA medications, thiopurines or systemic corticosteroids around the time of conception did not have an increased risk of infections. In the first year of life, the overall risk of childhood infections was not significantly increased after fathers' use of anti-TNF-α agents. During the second and third years of life, the overall risk of childhood infections was not increased after fathers' use of 5-ASA medications, thiopurines or anti-TNF-a agents. The overall risk of childhood infections during the second and third years of life was not significantly increased after fathers' use of corticosteroids.

Our former Danish studies as well as a recent study by Meserve et al. have shown that there is no increased risk of adverse birth outcomes of the children of fathers with IBD and other immune-mediated inflammatory diseases who used thiopurines, methotrexate and biologics just prior to conception.[9–12] Winter et al. found no difference in preterm birth, congenital abnormalities (CAs) or SGA in the children of fathers who used methotrexate within 3 months prior to conception.[10] Larsen et al. found no difference in preterm birth or CAs but did find a non-statistically significant increase in SGA in the children of fathers who used anti-TNF medications immediately prior to conception.[12] Nørgård et al. found no difference in preterm birth, CAs or SGA in the children of fathers who used mercaptopurine/azathioprine prior to conception.[11] In the study by Meserve et al., the authors report the first outcomes of paternal vedolizumab and ustekinumab use as well as additional data on the safety of paternal preconception use of methotrexate, thiopurines, and anti-TNF medications.[13] Similar to the Danish studies, Meserve et al. found no increased risk of preterm birth, low birth weight or CAs in infants of fathers who had taken thiopurines, methotrexate, or biologics within 3 months before conception. In the only previous study that examined the long-term outcomes of the children of fathers exposed to thiopurines or methotrexate just prior to conception, Friedman et al. examine the risk of childhood malignancies, autism spectrum disorder/schizophrenia and attention deficit hyperactivity disorder. With a median follow-up time of 6.7 years for exposed children and

TABLE 2 Crude and adjusted hazard ratio, with 95% confidence interval (CI), for the first infection in children fathered by men treated with IBD medications within 3 months prior to conception

	Overall infections exposed to children		Overall infections not exposed to children		Hazard ratio, (95% CI)	
Father's medication	***N* (%), event**	***N*, Total**	***N* (%), events**	***N*, Total**	**Crude**	**Adjusted[a]**
0–1 year						
5-ASA	274 (12.6)	2178	1260 (16.2)	7771	0.76 (0.67–0.87)	0.78 (0.66–0.91)[b]
Thiopurines	129 (15.3)	843	1405 (15.4)	9106	0.99 (0.83–1.19)	0.89 (0.73–1.09)[c]
Systemic corticosteroids	53 (12.7)	417	1481 (15.5)	9532	0.81 (0.61–1.06)	0.95 (0.70–1.29)[d]
Anti-TNF-α agents	93 (21.3)	436	1441 (15.1)	9513	1.48 (1.20–1.82)	1.17 (0.94–1.46)[e]
1–3 years						
5-ASA	333 (17.6)	1890	1138 (17.6)	6466	1.00 (0.89–1.13)	0.97 (0.83–1.13)[b]
Thiopurines	120 (16.9)	709	1351 (17.7)	7649	0.96 (0.79–1.15)	0.87 (0.71–1.07)[c]
Systemic Corticosteroids	74 (20.6)	360	1397 (17.5)	7996	1.20 (0.95–1.52)	1.25 (0.94–1.65)[d]
Anti-TNF-α agents	57 (16.7)	342	1414 (17.6)	8014	0.94 (0.72–1.23)	0.79 (0.60–1.03)[e]

[a]Table 1 variables: paternal age at birth, Charlson Comorbidity index of the father, type of IBD of the father, maternal age at birth, maternal Charlson Comorbidity, maternal BMI, maternal smoking status, the child's birth year, sex of the child, small for gestational and preterm birth.

[b]Adjusted for Thiopurines, Systemic Corticosteroids, Anti-TNF-α agents and Table 1 variables.

[c]Adjusted for 5-ASA, Systemic Corticosteroids, Anti-TNF-α agents and Table 1 variables.

[d]Adjusted for 5-ASA, Thiopurines, Anti-TNF-α agents and Table 1 variables.

[e]Adjusted for 5-ASA, Thiopurines, Systemic Corticosteroids and Table 1 variables.

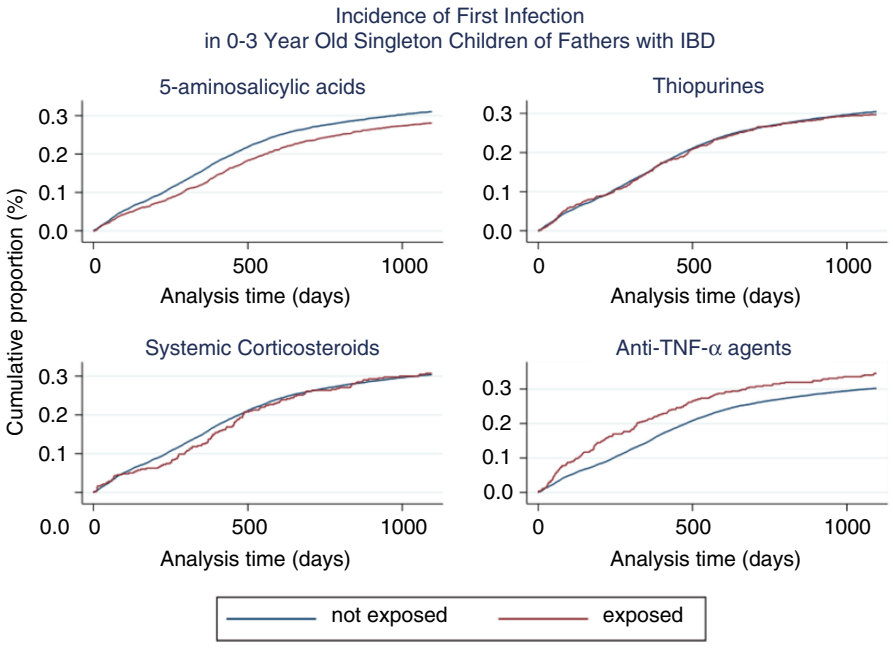

FIGURE 1 The cumulative proportion of infections from time of birth to 3 years of age according to the time of the first infection of any kind, in children exposed to paternal IBD medications.

9.9 years for unexposed, there were no increased adverse outcomes in the exposed group.[14] Our current study also examines longer-term outcomes in exposed children. We expanded our research to include the risk of childhood infections after paternal exposure to 5-ASAs, thiopurines, systemic corticosteroids and anti-TNF-a agents. Our results are overall reassuring, as fathers' use of anti-inflammatory/immunosuppressive medications before the time of conception was not significantly associated with childhood infections. The most important strength of our study is the nationwide-based design providing cohorts of fathers exposed to each class of IBD medication as well as a control group of fathers with IBD and no medication exposure. It is an important strength that we had longer-term follow-up of exposed and unexposed children and infectious outcomes. We have valid information from the Danish National Patient Registry on diagnoses and procedure codes for biologic medications, from the Medical Birth Registry on key birth-related variables as well as data

on filled prescriptions from the Nationwide Prescription Registry. We did not have information on drug compliance, and some could argue that paternal information on drug exposure is misclassified. However, even if some children were misclassified with regards to paternal drug exposure, it would lead to a non-differential misclassification giving bias towards the null hypothesis. We believe that it is a strength that information on paternal use of medications is not based on recall, as drug exposure based on self-reported use may lead to recall bias or under-ascertainment. We have valid measurements on our outcomes.[15,25] We were able to adjust for several important confounders including paternal age at birth, paternal Charlson Comorbidity index, type of IBD of the father, maternal age at birth, maternal Charlson Comorbidity, maternal BMI, maternal smoking status, the child's birth year, sex of the child, small for gestational and preterm birth. In addition, we mutually adjusted for the medication exposures. This study also has limitations. We could not examine a dose–response effect as we had no information on medication dosages. Although we did adjust for multiple confounders, we did not have information on disease activity as this is a nationwide database study and we did not have access to the many individual charts. While we did not examine the effect of steroids directly, we did adjust our analyses for systemic corticosteroid use, which is a proxy for disease activity. It is possible, however, that we may have missed an effect of a disease flare at conception on the offspring. Accurate recording of disease activity can only be done in the context of a prospective study. Additionally, we had no data on socioeconomic factors which may have influenced childhood infections. A small proportion of the registered fathers might not be the biological father of the child. However, there is no reason to believe that this is different among the exposed and unexposed groups. Theoretically, other confounders might have affected our results, and in an observational study like this, one can never rule out an impact of unknown or residual confounding.

Although there are a number of studies on the long-term outcomes of children exposed to thiopurines and biologics in utero, there is little information on the paternal effect.[26–30] The data on short-term child outcomes after paternal medication exposure is emerging, but there is a large research gap concerning the long-term health consequences of exposed children.[30] To the best of our knowledge, this study is the first to examine the longer-term risk of infections in the children of fathers who used IBD medications just prior to conception. These results fill an important research gap regarding the safety of expectant fathers' use of anti-inflammatory/immunosuppressive medications. Future research should be focused on cohort studies with a long follow-up time to understand how the paternal disease affects offspring across their lifespan.

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AUTHORSHIP

All authors approved the final version of this manuscript.

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Author contributions: **Sonia Friedman**: conceptualization; dataCuration; investigation; methodology; supervision; validation; writing – review and editing. **Olav Sivertsen Garvik**: Data curation (lead); formal analysis (lead); methodology (supporting); software (supporting); validation (lead); writing – review and editing (supporting). **Jan Nielsen**: Data curation (supporting); formal analysis(supporting); methodology (supporting); software (supporting); validation (supporting); writing – review and editing(supporting). **Bente Mertz Nørgård**: Conceptualization (equal); data curation (equal); investigation (equal); methodology(supporting); project administration (equal); supervision (equal); validation (supporting); writing – review and editing (supporting).

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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