

# Minor impact on fertility in men with inflammatory bowel disease: a national cohort study from Sweden

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## Summary

**Background:** Onset of inflammatory bowel disease (IBD) in men is most common during reproductive age, but little is known about the impact on fertility. Previous studies of fertility in men were small.

**Aim:** To assess fertility among young men with IBD

**Methods:** Fertility was assessed in a national cohort of men with IBD aged 15–44 years in 1964–2014, identified from the Swedish National Patient Register, and in a reference cohort matched for age and place of residence (ratio 1:5). Information about childbirths was found in the Swedish Multi-Generation Register. Patients with indeterminate colitis or inconsistent IBD coding were classified as IBD-unclassified (IBD-U).

**Results:** The cohorts included 29,104 men with IBD and 140,901 matched individuals. IBD patients had a lower fertility rate (number of births per 1000 person years) compared with the matched individuals; 1.28 (SD 1.27) versus 1.35 (SD 1.31;  $p < 0.001$ ). Fertility was somewhat impaired in all IBD subtypes compared with the matched cohort; ulcerative colitis (UC) (hazard ratio [HR] 0.93, 95% CI 0.91–0.96), Crohn's disease (CD) (HR 0.95, 95% CI 0.92–0.98) and IBD-U 0.92, 95% CI 0.89–0.95. The cumulated total parity and the parity progression were also decreased for all IBD subtypes. Within the IBD cohort disease severity, intensity of medical treatment (CD) and bowel surgery (IBD-U) were further associated with impaired fertility.

**Conclusions:** This nationwide cohort study shows only slightly impaired fertility in men with IBD.

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## 1 | INTRODUCTION

Inflammatory bowel disease (IBD) often presents during adolescence or early adulthood<sup>1</sup> and reproductive issues are for this reason of great importance to these patients. Fertility (i.e. the number of children actually born) is decreased in women with IBD,<sup>2</sup> while fertility in men has been less studied.<sup>3</sup> Results from previous research suggest a reduced fertility in men with Crohn's disease (CD)<sup>4–6</sup> but normal fertility in men with ulcerative colitis (UC).<sup>5,6</sup>

The cause of the reduced fertility in men with IBD is not clear, both reduced fecundity (i.e., the biological reproductive capacity) and psychosocial factors may be the contributing factors. Active inflammation, poor nutrition, alcohol habits, smoking, sexual dysfunction, medication, surgery, depression and voluntary childlessness are proposed contributing factors.<sup>7,8</sup>

The impact of IBD on male fertility is however largely unknown—previous population-based studies are outdated, were of limited size and had methodological weaknesses.<sup>9</sup> The objective of this study was to examine fertility in a large cohort of unselected men with IBD.

## 2 | METHODS

### 2.1 | Concepts of fertility

There is a conceptual confusion regarding the terminology of reproduction. In demographic and epidemiological contexts, however, fertility indicates the outcome of reproduction (number of live births) rather than the ability to have children.<sup>10</sup> From this perspective the physiological ability to have children is termed fecundity. While fertility can be measured, fecundity cannot be. A further aspect of reproduction is fecundability, which is the probability of becoming pregnant given regular unprotected intercourse, measured as time to pregnancy or a couple's probability of conceiving in one menstrual cycle. Fertility rate is the number of live births in a year per 1000 men of reproductive age. Parity is the number of children a man has fathered, while parity progression is the proportion of men who progress from one parity to the next.

### 2.2 | Data sources

All Swedish residents are assigned a unique personal identification number. This identity number is used in all official registers, thereby enabling linkage between them.<sup>11</sup> The Swedish National Patient Register (NPR) contains information on discharge diagnoses and surgical interventions for all hospital admissions since 1964, reaching full national coverage by 1987. Since 2001 details on all outpatient specialist care have been included as well.<sup>12</sup> The Swedish Multi-Generation Register (MGR) contains information on children born in Sweden since 1932. In the register the child's paternity automatically

applies to the husband of the mother at the time of birth or “by acknowledgment” for unmarried mothers. Adoption or other nonbiological relations are marked in the register and were excluded from the analyses.<sup>13</sup> The Prescribed Drug Register (PDR) provides information on all prescriptions since 2005, but not on drugs given in hospital. Information about socioeconomic status (SES) was obtained from the Longitudinal Integrated database for Health Insurance and Labour market studies (LISA) established by Statistics Sweden (SCB) in 1990.

### 2.3 | Study population

We identified a cohort of all male patients with  $\geq 2$  entries of an IBD diagnosis in the NPR during the study period 1964–2014. ICD-codes for UC, CD and indeterminate colitis (IC) were used (Data S1).

It is not always straightforward to decide whether patients with IBD have UC or CD in the clinical setting. The term IC should be reserved for patients without a definitive diagnosis even after complete histological analysis of a colectomy specimen.<sup>14</sup> The term IBD unclassified (IBD-U) is increasingly used for patients with their colon still in place where the clinical presentation is atypical or varying over time. For some patients, the IBD diagnosis was inconsistent at successive discharges during the study period. From several schemes proposed to categorise these patients from register data we used a slightly modified variant of the classification promoted by Everhov et al.<sup>15</sup>

The final IBD diagnosis was defined as UC or CD in patients who had a consistent IBD discharge diagnosis. Patients with an initial diagnosis of IC, followed by a later consistent diagnosis of UC or CD were accepted as having UC or CD, respectively. Patients with a consistent IC diagnosis as well as patients with any other combination of UC, CD or IC diagnoses were defined as having IBD-U as the final diagnosis. In accordance with Everhov et al. we also classified UC patients having an additional ICD code for mainly CD-related conditions, like perianal disease and small bowel involvement, as having IBD-U in order to minimise misclassification and keep the UC and CD cohorts as consistent as possible.

Information about children born to men in the two cohorts was obtained through linkage with the MGR. The demography and the characteristics of the cohorts, as well as the parity at diagnosis, the number of children born during follow-up and the achieved parity at the end of follow-up were assessed. Information on SES, obtained from LISA, was used to investigate impact of socioeconomic status.

We analysed the impact of four parameters reflecting the severity of disease - hospital admissions, bowel resections, the intensity of medical treatment and perianal disease. IBD patients with a severe flare are usually admitted to hospital in order to receive the most potent medical treatment (e.g. intravenous steroids or infliximab), therefore the order of hospital admissions with a diagnostic code for IBD since the first date of diagnosis was used as a time-varying covariate to describe the severity of disease. Bowel resections

were identified using intervention codes in the NPR (Data S2). The order of procedures performed was used as a time varying covariate to analyse the possible impact on fertility. Perianal disease was identified using diagnostic codes for anal fistula, abscess, or fissure, and the associated intervention codes (Data S3). Information on prescribed medical treatment was found in the PDR. Medical treatment was grouped into low (no treatment, rectal administered anti-inflammatory drugs or systemic corticosteroids), medium (immunosuppressing drugs) and high intensity treatment (biological therapies) (Data S4). The highest treatment intensity received during the study period was used to determine the severity of disease for each IBD patient.

For comparison Statistics Sweden (SCB) identified a cohort of men (1:5) from the general population matched for age. As the NPR initially did not have complete national coverage, we also matched for place of residence at date of diagnosis in order to avoid ascertainment bias. A vast majority (92%) of the matching sets had five matched individuals for each IBD patient. In the remaining 8% the number of matched individuals was reduced due to lack of eligible individuals, but each IBD patient had at least one matched individual.

## 2.4 | Statistical analysis

The characteristics were assessed for the cohorts and sub-cohorts, for example, age at diagnosis, duration of follow-up, parity at baseline, achieved parity at end of follow-up and proportion of childless men at baseline and at the end of follow-up. For the matched cohorts the follow-up of the occurrence of pregnancy of the female partner resulting in childbirth started when the IBD-patients were diagnosed and ended when they turned 45 years or on 31 December 2014, whichever occurred earliest.

The fertility of the men in the cohorts, expressed as the rate of childbirth over time since diagnosis, was compared by Cox regression, with adjustment for covariates and using Andersen-Gill models to allow for recurrent events like the multiple births of children. The stratification of sets of IBD-patients and matched individuals allowed for different baselines but assumed equal hazard ratios across strata. The impact of admissions to hospital and intestinal resections were analysed as time varying covariates, with truncation at  $\geq 4$  admissions and  $\geq 6$  procedures, respectively. For the order of admissions most IBD-patients are diagnosed at the first admission, but some may also have their diagnosis as outpatients before a possible later admission. The analysis of the impact of the intensity of medical treatment was limited to sets matched in 2005 and later as information on prescribed drugs was available first from 2005. The parity progression ratio, the proportion of men with IBD who progress from one parity to the next compared with the matched cohort, was analysed using logistic regression.

Sensitivity analyses were performed to investigate any impact of socioeconomic status (SES) at diagnosis, deciles of disposable income and educational level were used. Information on SES was

available from 1990, thus, only sets matched in 1990 and later were used in these analyses.

Trends were analysed with likelihood ratio test for models with and without interaction terms, and with the Mantel-Haenszel test for trend. Differences in proportions were analysed with the chi square test. A  $p < 0.05$  was considered as a statistically significant difference. All analyses were performed in Stata 15 (Stata Statistical Software: Release 15; StataCorp LLC).

The study was approved by the Regional ethical review board in Linköping (registration number of ethical approvals including amendments: 2011/419-31, 2014/226-32, 2014/492-32 and 2015/123-32).

## 3 | RESULTS

### 3.1 | Study population

A cohort of 29,104 men with  $\geq 2$  entries of an IBD diagnosis was identified from the NPR (UC 13,966, CD 8283 and IBD-U 6855). The matched reference cohort (1:5) included 140,901 men (Table 1). The mean age at IBD diagnosis, and thus age at inclusion in the study, was 27.9 (SD 9.6) years and the mean follow-up time was 10.4 (SD 7.5) years. Men with UC were somewhat older and had a higher parity at diagnosis, compared with men with CD and IBD-U. Patients with CD were younger than other IBD patients at first surgery and more likely to be exposed to bowel surgery (45.1%) than patients with IBD-U (36.6%) and UC (17.8%) ( $p < 0.001$ ).

A total of 17,627 births were linked to men with IBD during the study period, corresponding to a mean achieved parity at end of follow-up of 1.28 (SD 1.27) births, somewhat lower than in the matched individuals at 1.35 (SD 1.35) ( $p < 0.001$ ). The achieved parity at end of follow-up was particularly affected by CD (mean 1.25 SD, 1.29) ( $p < 0.001$ ) and IBD-U (mean 1.28, SD 1.28) ( $p < 0.001$ ), but also to a lesser extent by UC (mean 1.30, SD 1.26) ( $p < 0.001$ ).

The proportion of childless men at the end of follow-up was lower among men with IBD than in the reference cohort (37.9 vs. 39.6%,  $p < 0.001$ ). Corresponding figures for the IBD subtypes reveal higher risk for childlessness in UC (38.4 vs. 36.5%,  $p < 0.001$ ) and in IBD-U (39.9 vs. 37.6%,  $p < 0.001$ ), whereas no statistically significant difference was seen in CD patients and their matched individuals (41.5 vs. 40.4%,  $p < 0.055$ ).

### 3.2 | Impact in IBD subsets

Compared with their matched individuals, fertility was decreased in all subtypes of IBD, with HR 0.92 (95% confidence interval [CI] 0.89–0.95) in IBD-U, HR 0.93 (95% CI 0.91–0.96) in UC and HR 0.95 (95% CI 0.92–0.98) in CD (Table 2). In analysis of fertility at different patient ages, men with UC and IBD-U had a markedly depressed fertility at the lowest ages compared with the matched

**TABLE 1** Demography and characteristics of the study cohorts of male inflammatory bowel disease patients from the Swedish patient register 1964 to 2014 and a population-based matched cohort

Characteristics	Matched cohort	IBD cohort	IBD sub cohorts		
			UC	CD	IBD-U
Patient. No	140,901	29,104	13,966	8283	6855
Age at inclusion, years, mean (SD)	27.8 (9.5)	27.8 (9.5)	29.0 (9.2)	26.8 (9.5)	26.5 (9.7)
Follow-up time, years, mean (SD)	10.4 (7.5)	10.5 (7.5)	9.6 (7.0)	11.0 (8.0)	11.9 (7.7)
Bowel surgery, no. (proportion)		8731 (5.1)	2489 (17.8)	3733 (45.1)	2509 (36.6)
Age at first bowel surgery, mean (SD)		32.1 (10.8)	34.4 (10.9)	30.3 (10.0)	32.7 (11.2)
Age at first child, years, mean (SD)	29.1 (5.4)	29.3 (5.4)	29.6 (5.4)	29.0 (5.5)	29.3 (5.4)
Parity at baseline, mean (SD)	0.70 (1.08)	0.68 (1.06)	0.74 (1.09)	0.63 (1.03)	0.60 (1.02)
Achieved parity at end of follow-up, mean (SD)	1.35 (1.31)	1.28 (1.27)	1.30 (1.26)	1.25 (1.29)	1.28 (1.28)
Childless at baseline, no. (proportion)	90,148 (64.0%)	18,851 (64.8%)	8613 (61.7%)	5553 (67.0%)	4685 (68.3%)
No child during follow-up, no. (proportion)	89,314 (63.4%)	18,908 (65.0%)	9289 (66.5%)	5362 (64.7%)	4257 (62.1%)
Childless at end of follow-up, no. (proportion)	53,367 (37.9%)	11,536 (39.6%)	5359 (38.4%)	3439 (41.5%)	2738 (39.9%)
Year of inclusion, no. (proportion)					
1964–1973	6844 (4.9%)	1479 (5.1%)	485 (3.5%)	588 (7.1%)	406 (5.9%)
1974–1983	17,578 (12.5%)	3603 (12.4%)	1433 (10.3%)	1230 (14.8%)	940 (13.7%)
1984–1993	23,764 (16.9%)	4883 (16.8%)	2179 (15.6%)	1401 (16.9%)	1303 (19.0%)
1994–2003	39,122 (27.8%)	8063 (27.7%)	4067 (29.1%)	1878 (22.7%)	2118 (30.9%)
2004–2014	53,595 (38.0%)	11,076 (38.1%)	5802 (41.5%)	3186 (38.5%)	2088 (30.5%)

Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel disease; IBD-U, IBD unclassified; UC, ulcerative colitis.

set. The impact was less pronounced with increasing age (test for trend, UC  $p < 0.001$  and IBD-U  $p < 0.008$ ). A similar trend was seen in CD, although not statistically significant. In an analysis of fertility for each decade of the long study period, no apparent secular trend was observed.

Inclusion of socioeconomic status use in multivariable analyses in follow-up data from July 2005 did not change the HR, suggesting that there is no difference in impact of these variables between the IBD patients and matched individuals [data not shown].

Any admission to hospital due to IBD was associated with a lower chance of becoming father compared to the matched population. In UC and IBD-U, but not in CD, there was a trend towards decreasing fertility with increasing number of hospital admissions (test for trend,  $p < 0.012$  and  $p < 0.001$ , respectively) (Table 3).

An increasing number of bowel resections was associated with a reduced fertility for men with IBD-U compared to the matched population (test for trend,  $p < 0.034$ ). No such association was seen in UC or CD.

In the subset of the IBD cohort with available data regarding drug treatment (from 2005 onwards), there was a tendency for higher treatment intensity to affect fertility more. Possibly due to the small sample, this trend was only statistically significant in CD (test for trend,  $p < 0.033$ ).

Perianal disease in CD had no clear effect on male fertility, HR was 0.93 (95% CI 0.86–1.00) with perianal disease and 0.95 (95% CI 0.92–0.98) without.

### 3.3 | Parity progression ratio

The proportion of men progressing from one parity to the next after diagnosis, known as parity progression ratio, was decreased in all subtypes of IBD (Table 4). The most pronounced impact was observed for patients with low parity at disease onset (no or one child). In particular childless patients, prior to being diagnosed with UC or IBD-U, were much less likely to become father twice.

## 4 | DISCUSSION

A slightly reduced fertility in men with all subtypes of IBD is the main finding in this report. This adds new knowledge as the impact of IBD on male fertility is previously largely unknown. The terms used to describe male reproductive capacity are somewhat ambiguous and a general consensus does not exist.<sup>10</sup> Fecundity is the biologic capacity to reproduce, and cannot be measured although several indirect markers can be used. Fecundability is a couple's probability of conceiving given regular unprotected intercourse, measured as time to pregnancy. There is no way of measuring the male component directly. Fertility, in its demographic meaning, is the number of children born and is partially driven by semen quality in addition to the male's role in shaping the desire for a given family size. From population registers, fertility numbers can be calculated, but changes in fertility does not always reflect fecundity fairly, as fertility is affected by many environmental factors.<sup>16</sup>

**TABLE 2** Fertility for men with subtypes of inflammatory bowel disease compared with matched individuals, expressed as hazard ratio in strata of age and time periods in univariable analysis

	UC			CD			IBD-U		
	HR	95% CI	p-value <sup>a</sup>	HR	95% CI	p-value <sup>a</sup>	HR	95% CI	p-value <sup>a</sup>
Overall	0.93	0.91–0.96		0.95	0.92–0.98		0.92	0.89–0.95	
Age			0.001			0.063			0.008
15–19 years	0.46	0.26–0.79		0.79	0.48–1.30		0.43	0.23–0.82	
20–24 years	0.71	0.64–0.79		0.83	0.74–0.92		0.69	0.61–0.78	
25–29 years	0.89	0.85–0.94		0.92	0.87–0.98		0.87	0.82–0.93	
30–34 years	0.94	0.90–0.98		0.94	0.90–1.00		0.96	0.90–1.01	
35–39 years	0.99	0.94–1.04		1.01	0.95–1.08		1.00	0.93–1.07	
40–44 years	1.00	0.92–1.09		1.02	0.92–1.14		0.93	0.83–1.04	
Time-periods			0.091			0.127			0.178
1964–1973	0.95	0.85–1.05		1.01	0.92–1.11		0.94	0.83–1.04	
1974–1983	0.91	0.85–0.97		0.99	0.92–1.05		0.88	0.81–0.95	
1984–1993	0.89	0.84–0.94		0.94	0.88–1.00		0.87	0.81–0.92	
1994–2003	0.96	0.92–1.00		0.92	0.87–0.98		0.96	0.90–1.01	
2004–2014	0.96	0.91–1.01		0.95	0.88–1.02		0.96	0.88–1.05	

Note: HR is Hazard Ratio with 95% confidence interval (95% CI).

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, IBD unclassified; UC, ulcerative colitis.

<sup>a</sup>The test for trend is a Likelihood Ratio test comparing models with and without interaction.

Only a few population-based studies of fertility in men with IBD have been reported, based on a few hundred patients in total, with data collected from clinical records and without a population-based reference group.<sup>9</sup> Our nationwide study included 29,104 men with IBD, by far making it the largest study of fertility in men with IBD. The long average follow-up time and data covering the entire reproductive history of the included population allows for valid estimates of fertility. The population-based design including a matched cohort minimise the risk for selection bias that are usually present in hospital-based series. It also controls for possible biases from fertility issues that are unrelated to IBD and equally distributed in the matched cohorts, like female fertility problems and the secular changes in fertility. The impaired fertility in CD is consistent with previous studies,<sup>4–6</sup> but according to the present results the impact is not as profound as previously reported.<sup>9</sup> Earlier studies on fertility in UC show partially contradictory results,<sup>5,6,17</sup> while our results demonstrate an evident impairment.

It is well-known that colitis is sometimes difficult to categorise as either UC or CD. The disease may present with characteristics that are mixed or that may change over time. Consequently, the registered diagnosis sometimes varies over time. The subgroup of patients who do not consistently meet the diagnostic criteria for UC or CD is variably classified in the literature.<sup>18</sup> The term IBD-U has been proposed for patients lacking characteristic features of UC or CD.<sup>14</sup> Of the many alternative classification schemes proposed, we used a mildly modified variant of the classification recently suggested and validated by Everhov et al.<sup>15</sup> With this approach we were especially keen to avoid contamination from any misclassified UC and CD patients. The UC and CD cohorts are therefore as clean and robust

as can reasonably be achieved. By comparison, the IBD-U cohort is composed of a mixture of IBD subtypes, with a clinical presentation that has been difficult to refer to any of the UC and CD diagnoses. In the present study, the fertility in IBD-U was reduced to about the same extent as in UC and CD.

There are several findings that support a biological impact on reproductive ability in men, that is, that impaired fecundity is at least partially responsible for the reduced fertility. Female partners to men with an IBD diagnosis are for example more likely to use assisted reproductive techniques<sup>19</sup> and infertility counselling is more common among men with CD.<sup>20</sup> Also, increased use of medication for erectile dysfunction<sup>21</sup> and elevated rates of sexual dysfunction<sup>22</sup> among men with IBD have been reported. Underlying mechanisms explaining the reduced fecundity may include poor nutritional status which can reduce fertility due to zinc deficiency leading to reduced testicular function. Low testosterone levels, associated with disease activity and treatment, have been reported in men with IBD. Furthermore, anti-sperm antibodies have been observed in men with IBD, but the clinical relevance of this is unclear.<sup>3</sup>

Apart from physiological factors, voluntary birth control could contribute to the reduced fertility in male IBD patients for reasons such as fear of congenital abnormalities caused by the disease, concerns of transmitting IBD and concerns of teratogenicity of medications.<sup>17,23</sup> Based on our register data, it is not possible to distinguish to what extent the reduced fertility relates to voluntary childlessness. However, based on findings in previous studies, it can be assumed that it is a significant proportion.<sup>24</sup>

Consistent with previous studies, increasing severity of the disease was associated with decreasing fertility, with slightly

**TABLE 3** Impact of disease severity on male fertility for inflammatory bowel disease subtypes, expressed as hazard ratio for giving birth in relation to the order of hospital admissions during follow-up, intensity of medical treatment and bowel surgery, compared with matched individuals, with adjustment for age and year at diagnosis in multivariable analysis. The order of admission and number of bowel resections were analysed as time-varying covariates

	UC				CD				IBD-U			
	No.	HR	95% CI	p-value	No.	HR	95% CI	p-value	No.	HR	95% CI	p-value
Order of admissions				0.012 <sup>a</sup>				0.266 <sup>a</sup>				<0.001 <sup>a</sup>
0	7734	0.99	0.95–1.03	0.615	3594	0.98	0.91–1.05	0.602	2817	0.99	0.92–1.06	0.744
1	7512	0.90	0.85–0.94	<0.001	5726	0.95	0.90–1.01	0.107	4931	0.97	0.91–1.04	0.428
2	4753	0.94	0.88–1.00	0.057	3915	0.98	0.91–1.05	0.552	3693	0.88	0.81–0.96	0.004
3	3078	0.88	0.81–0.96	0.003	2619	0.97	0.89–1.07	0.561	2801	0.93	0.84–1.03	1.172
>3	2120	0.90	0.85–0.96	0.002	1914	0.91	0.86–0.97	0.005	2292	0.86	0.81–0.91	<0.001
No. of bowel procedures				0.958 <sup>a</sup>				0.689 <sup>a</sup>				0.034 <sup>a</sup>
0	13,681	0.93	0.91–0.96	<0.001	6951	0.93	0.89–0.97	0.001	6564	0.93	0.90–0.97	0.001
1	2107	0.95	0.87–1.03	0.203	3481	1.01	0.97–1.06	0.580	2152	0.91	0.84–0.98	0.015
2	922	0.90	0.81–1.00	0.058	951	0.86	0.77–0.97	0.013	960	0.84	0.75–0.93	0.002
3	145	1.10	0.80–1.50	0.552	324	0.94	0.74–1.19	0.621	278	0.84	0.66–1.06	0.140
>3	38	0.87	0.51–1.48	0.600	105	0.89	0.65–1.21	0.462	92	0.87	0.61–1.22	0.413
Intensity of treatment <sup>b</sup>				0.336 <sup>a</sup>				0.033 <sup>a</sup>				0.588 <sup>a</sup>
Low	1366	0.96	0.90–1.02	0.144	250	1.01	0.90–1.13	0.877	254	0.90	0.81–1.01	0.064
Medium	272	0.90	0.69–1.18	0.449	180	0.89	0.77–1.05	0.156	51	1.09	0.82–1.47	0.547
High	114	0.68	0.32–1.43	0.287	82	0.79	0.62–1.01	0.054	22	0.89	0.54–1.47	0.642

Note: Hazard ratio (HR) with 95% confidence interval (95% CI).

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, IBD unclassified; UC, ulcerative colitis.

<sup>a</sup>The test for trend is a Likelihood Ratio test comparing models with and without interaction.

<sup>b</sup>Medications only available from the Prescribed Drug Register from 2005 and onwards.



**TABLE 4** Male parity progression ratio (the probability of having one or two additional children) according to parity at diagnosis and subtypes of inflammatory bowel disease, compared with matched individuals

Parity at diagnosis	Parity progression	UC			CD			IBD-U		
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Para 0	+1	0.92	0.88–0.96	0.001	0.93	0.88–0.99	0.020	0.91	0.85–0.97	0.003
	+2	0.88	0.83–0.93	<0.001	0.92	0.86–0.98	0.011	0.87	0.81–0.94	<0.001
Para 1	+1	0.94	0.85–1.04	0.218	0.97	0.84–1.11	0.627	0.91	0.78–1.07	0.258
	+2	0.88	0.76–1.02	0.086	0.99	0.81–1.20	0.903	0.93	0.75–1.14	0.475
Para 2+	+1	1.03	0.98–1.09	0.290	1.01	0.93–1.09	0.839	1.02	0.93–1.11	0.689
	+2	0.80	0.66–0.98	0.028	1.04	0.82–1.32	0.755	0.84	0.64–1.11	0.214

Note: Odds ratio (OR) with 95% confidence interval (95% CI).

No child at baseline (para 0), one child at baseline (para 1) and two or more children at baseline (para 2+).

Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel disease; IBD-U, IBD unclassified; UC, ulcerative colitis.

different patterns, in all subtypes of IBD.<sup>19</sup> It has been shown that men in clinical remission or with mild symptoms have a similar incidence of erectile dysfunction as healthy controls, whereas the occurrence is higher in men with active IBD<sup>25</sup> with increased bowel symptoms at flares as a main reason.<sup>26</sup> Moreover, disease activity, with pro-inflammatory cytokines and reactive oxygen species as mediators,<sup>7</sup> seems to affect both reproductive ability and sexual function.<sup>3,19,25,27</sup> Sulfasalazine reversibly reduces male fertility and methotrexate and sulfasalazine have been associated with erectile dysfunction in some reports. No other medications used in IBD is known to affect fertility in males.<sup>8</sup> In the very limited part of the study population where information on prescribed medications were available, more intensive medical treatment was associated with impaired fertility in CD. Of note, data on in-hospital treatments is not included in the Prescribed Drug Register and thus not included in these estimates.

The number of intestinal resections was associated with fertility in IBD-U. It is not clear however to what extent the surgery itself causes fertility problems, or rather serves as a surrogate marker for severe disease. Previous data on the effect of surgery on fertility rates in men with IBD are limited, but it is well-established that pelvic surgery for any reason may lead to erectile or ejaculatory problems.<sup>28</sup> Bowel surgery in UC and CD had however no negative effect on fertility in the present study, consistent with previous findings.<sup>8,29</sup>

During the long study period fertility patterns have changed in the society, which probably has influenced the desire to have children among men with IBD. We have performed separate analyses stratifying for the time-period, the year and age at disease onset but no temporal trend was identified when fertility was analysed in different decades. It cannot be ruled out that the stable fertility rates are the result of several factors that affect fertility in the opposite direction, for instance treatments for IBD have changed profoundly over the decades.

Although a population-based study has many advantages, there are some limitations. For example, the NPR contains no information on tobacco use in the males or their female partner. Smoking impairs fertility, but may also affect the course of IBD.<sup>30</sup> Smoking may therefore be differentially distributed in the cohorts. It is also possible

that body mass index (BMI) is differently distributed between the cohorts, an additional factor that is known to affect fertility but unavailable for both male and their female partner from the registries. Neither were information about age and comorbidity of the female partners available. Another limitation with the present study was that the ICD coding has been revised four times during the study period. As a result, the same condition may have been coded differently at different times. Most obviously, there was no separate code for IC in ICD-9. Another point to be made was that the NPR reached complete national coverage first in 1987. However, this should not have an impact on the study results as the matched individuals were geographically tallied. Furthermore, the male fertility was assessed through the birth rates of the subject's partner, without considering possible paternal discrepancy or misattributed paternity. Any bias arising from this is difficult to predict as non-paternity rates vary greatly across populations (from 0.8 to 30%) and have been associated with different demographic factors.<sup>31</sup> However, there is no obvious reason to expect differences between IBD patients and matched individuals in this regard.

## 5 | CONCLUSION

This nationwide cohort study, conducted in a country with high IBD prevalence, shows only a slightly impaired fertility in men with IBD, measured as cumulated parity, fertility rate and parity progression. A decrease in fertility rate was associated with increasing number of hospital admissions in all of the IBD subcohorts. The intensity of treatment in CD and bowel resections in IBD-U were other factors associated with decreased fertility rates.

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## DISCLOSURES

The authors declare that they have no conflict of interest. This manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere.

## WRITING ASSISTANCE

None.

## AUTHOR CONTRIBUTIONS

**Emma Druvefors:** Conceptualization (equal); data curation (equal); funding acquisition (equal); methodology (equal); project administration (equal); visualization (supporting); writing – original draft (lead).

**Roland Andersson:** Conceptualization (supporting); data curation (equal); formal analysis (equal); funding acquisition (supporting); methodology (equal); project administration (supporting); supervision (lead); validation (lead); writing – review and editing (lead).

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## SUPPORTING INFORMATION

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