Childbearing is Associated with a Short-term Reduced Risk of Crohn's Disease in Mothers

Øystein Kravdal, Per Magnus, Bjørn Moum, and Marte Lie Høivik

Correspondence to Øystein Kravdal, Centre for Fertility and Health, Norwegian Institute of Public Health, PO Box 222 Skøyen, 0213 Oslo, Norway (e-mail: Oystein.Kravdal@fhi.no; phone 47 48020904; fax 47 22855035)

Author affiliations: Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway (Øystein Kravdal and Per Magnus); Department of Economics, University of Oslo, Norway (Øystein Kravdal); Institute of Health and Society, University of Oslo, Norway (Per Magnus); Department of Gastroenterology, Oslo University Hospital, Norway (Bjørn Moum and Marte Lie Høivik); and Faculty of Medicine, University of Oslo, Norway (Bjørn Moum and Marte Lie Høivik).

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Abbreviations: CD, Crohn's disease; CI, confidence interval; IBD, Inflammatory bowel disease; OR, odds ratio; PIN, personal identification number; UC, ulcerative colitis

ABSTRACT

The aim was to analyse the importance of childbearing for inflammatory bowel disease risks. Using data from the Norwegian Population Register and the Norwegian Patient Register, discrete-time hazard models for diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) were estimated for men and women of age 18-81 in 2011-2016. Year and various socio-demographic factors were controlled for. The data included 4304 CD and 8866 UC cases. Women whose youngest child was 0-4 years old had lower CD risk the following year than the childless (OR 0.73, CI: 0.62, 0.86). There was no such reduction in CD risk among fathers. Men whose youngest child was older than 20 had higher CD risk (OR 1.22, CI: 1.01, 1.49) and UC risk (OR 1.15, CI: 1.02, 1.30) than the childless. The UC risk was also increased among men whose youngest child was aged 0-4 (OR 1.14, CI: 1.02, 1.27). The short-term reduction of women's CD risk after a birth may reflect biological effects of the pregnancy. Alternatively, it may reflect residual confounding or lifestyle effects of parenthood that are of special relevance for CD in women. In particular, differences in use of oral contraception (not possible to control for) may contribute to the observed pattern.

Genetic predispositions play a role in the development of inflammatory bowel diseases (IBD), but several 'environmental' risk factors or protective factors have also been suggested (1-3). These include smoking, early-life use of antibiotics and exposure to harmless microorganisms, appendectomy, certain pathogenic infections, major life stressors, physical activity, UV-exposure, air pollution, and intake of dietary fibers, sugar, saturated fat, and animal proteins. Associations between oral contraception and disease incidence or progression indicate that sex hormones may be involved in the etiology (4-6). Sex differences in incidence (7) and variation in gastrointestinal symptoms among IBD patients during hormonal fluctuations (8-9) support such an idea. Further research about this would be valuable, because improved knowledge about disease etiology may have implications for treatment or prevention in the future.

The objective of this study was to examine the relationship between childbearing and IBD risks, which has received little attention (4,10). In principle, three types of mechanisms may contribute to a relationship (11,12): i) biological responses to pregnancies; ii) 'social' pathways, in particular effects of parenthood on lifestyle (broadly defined); and iii) confounding, i.e. joint determinants of childbearing and IBD risks not controlled for in the statistical model. The first mechanism is relevant only for women. Thus, if the relationship differs between the sexes, it would provide further support for the idea that (endogenous) sex hormones – or other biological factors linked to pregnancy – are involved in the development of the disease. Alternatively, sex differences in the relationship between reproduction and IBD risks may be a result of sex differences in the social effects or the confounding. As further discussed below, hormonal effects may be involved here also, through the use of contraception.

The analysis was based on nationwide register data from specialized health care and included 13,170 IBD cases. We controlled for well-known socio-demographic determinants

of reproductive behaviour with potential impact on IBD risks (confounders). Part of the analysis included, like earlier studies (4,10), a broad age group, but we also estimated models separately for quite young women and men, or took into account time since last birth, because one might expect some of the effects to operate in a relatively short term, while others also involve older children.

METHODS

Register sources

Our study was based on data extracted from three nationwide registers that were linked by means of a personal identification number (PIN). The last year covered by the data was 2016, except that births in 2016 were not included.

The Norwegian Population Register and the Education Database. Everyone who has lived in Norway at any time after 1964 has been assigned a PIN and included in the Norwegian Population Register. This register includes information about, for example, sex, year of birth, year of death (if applicable), marital status and municipality of residence (if living in the country) at the beginning of each of the years 1970-2016, and year of birth of all the live born children for whom the person is registered as the father or mother. The birth histories are derived from information on PINs of parents, which is available for almost everyone born in Norway after 1953 (13). Thus, the birth histories are almost complete for those born in 1935 or later (very few of whom had children before 1953), except that a small group of immigrants may have had children in the country of origin that they have not brought with them and that are therefore not registered.

The Education Database (operated by Statistics Norway) provides information about the highest educational level achieved at the beginning of each year since 1980.

The Norwegian Patient Register. The Norwegian Patient Register includes data on use of specialized health care for each individual in Norway from 2008. For each person in the selected birth cohorts (see below), we extracted the dates of all inpatient or outpatient hospital contacts where CD or UC was reported as main or secondary diagnosis, between 2008 and 2016. Corresponding information from private specialists who had contract with the regional health authorities, and therefore benefitted from public subsidies, was also extracted (although inclusion of these data had almost no impact on the results). For simplicity, all these contacts are referred to below as 'IBD hospital contacts'.

Study population

The study population included all persons registered in the Norwegian Population Register and born between 1935 and 1998. The 1935 limit was chosen because birth histories are not complete for older birth cohorts, and the1998 limit was chosen because individuals born in 1998 were 18 years old in 2016. Including younger individuals in an analysis of effects of reproduction would not be meaningful.

Outcomes

Our outcome was incident IBD, which we refer to also as diagnosis of IBD. It was defined as occurring in a year *t* if the individual had not been diagnosed earlier, and if there was at least one IBD hospital contact that year and at least two in total up to 2016. If the hospital contacts were registered with both UC and CD diagnoses, we considered the last of these as the correct diagnosis. The individual was reckoned as not having been diagnosed earlier if he or she had no IBD hospital contact during the years 2008 to *t*-1, and if that period included at least three years of residence in Norway. Being resident in a certain year was defined as living in the country both at the beginning of that year and at the beginning of the next year.

Statistical model

We estimated discrete-time hazard models for the odds that a person not diagnosed with IBD before the beginning of year *t* received a CD or UC diagnosis within that year. (This is a common type of event history analysis that has some advantages compared to the Cox model. (14)) More specifically, a series of one-year observations was constructed for each individual. The first observation was the first year after the 17th birthday when he or she had lived at least three years in Norway after the start of 2008 (cannot be earlier than 2011), and still had not had an IBD hospital contact. The last observation was 2016, the year of death, the year of the incident IBD (as defined above), or the year when there was an IBD hospital contact not followed by an additional IBD hospital contact in the same year or in any of the subsequent years up to 2016 - whatever occurred first. Thus, the observations for 2011 included the age group 18-76 (76 being the age of the 1935 cohort in 2011), while the observations for 2016 included the age group 18-81.

After having excluded the years when a person was not living in Norway (1.0 percent) or marital status was missing or not one of the standard categories (0.1 percent), logistic models for the odds of being diagnosed with CD or the odds of being diagnosed with UC were estimated from the remaining pool of one-year observations (see note to Table 1 about an alternative model).

Variables

The models included the number of children at the beginning of the respective one-year observations, and some of them included also duration since last birth (measured at that time). Additionally, they included variables known to be determinants of childbearing and possibly also influencing the IBD risks. All these control variables were categorical (see tables for category definitions). Some of them were time-varying and referred to the situation at the beginning of the respective one-year observations, while others were constant.

The time-varying variables were: age, calendar year (likely to be linked to the IBD risks at least because of our statistical design and definition of 'cases'; see Web Appendix 1), educational level, marital status, region of residence, and whether the municipality of residence was a city. Country of birth was a constant control variable taken from the Population Register. Parents' education (including a category for unknown, because parents were not identified for many of those born abroad or before 1953) was considered as constant, and referred to the situation in 2008. It was taken from the Education Database, making use of information about parents' PIN in the Population Register.

In a series of sensitivity tests we excluded some of these variables, or we changed the definition of the outcome or the inclusion requirements (see Results).

RESULTS

The risk of being diagnosed with CD was 14 percent lower for mothers than for childless women, while there was no such difference among men (see Table 1). In contrast, the UC risk was the same for mothers and childless women, but was 11 percent higher for fathers than childless men.

(Table 1 about here)

The point estimates suggested a sharper association between motherhood and the CD risk (OR 0.79) for the subgroup aged 18-44 than for the 18-81 group, while no association (OR 1.03) appeared for the age group 45-81 (see Table 2). For men, there was no significant association between parenthood and the CD risk in either of the age groups. Turning to UC, an elevated risk appeared among fathers in the youngest age group. The estimates were larger than 1 also for older women and men, but significance was not attained. The associations between the control variables and the IBD risks are described and briefly discussed in Web Appendix 1.

(Table 2 about here)

Parents within the age group 18-44 have, of course, younger children than those aged 45-81. To check the importance of time since last birth (as of time *t*; see Methods section) more explicitly, we included it in some models (Table 3). A significantly reduced CD risk compared to the childless appeared only for mothers whose youngest child was younger than five years old. The point estimates suggested a reduced risk also for those with a youngest child aged 5-9, 10-14 or 15-19, and if these categories were pooled together, significance at the 10 percent level was attained. Conversely, the UC risk was significantly higher in men whose youngest child was 0-4 year old, compared to the childless. Additionally, CD and UC risks were raised among men whose youngest child was older than 20. The estimates pointed in that direction for women as well, but were not significant.

(Table 3 about here)

One might suspect that the higher IBD risks among those with a youngest child older than 20 than those with a youngest child younger than 20 could be the result of a larger number of children among the latter. To check this possibility, parents were cross-classified by time since last birth, in two broad categories, and number of births (Table 4). No clear relationships between number of births and the IBD risks were seen, and given the number of children, all point estimates except one suggested that the IBD risks were highest if the youngest child was older than 20.

(Table 4 about here)

Several sensitivity tests were carried out. Results from these (Table 5) are referred to in the Discussion, with elaboration in Web Appendices 2 and 3.

(Table 5 about here)

DISCUSSION

In this nationwide cohort study including 13,170 IBD cases, we found that women whose youngest child was less than five years old had lower risk of being diagnosed with CD the following year than had those who were childless. Otherwise, IBD risks were not particularly low among parents. Both CD and UC risks were raised among men whose youngest child was older than 20, and there were weak indications in the same direction among women. Also, the UC risk was raised among men with a youngest child aged 0-4, so on the whole there was not a clear relationship between age of youngest child and UC risk among men. The results are robust to some alternative definitions of the outcome (Web Appendix 2), and there should not be much concern about over-controlling (Web Appendix 3).

In principle, three types of pathways may contribute to the observed relationships between reproduction and IBD risks (11,12):

- biological effects of pregnancies on IBD in the short or longer term,
- effects of having young or older children on lifestyle factors of importance for IBD risks (referred to as ‘social’ effects), and
- earlier health, social resources, lifestyle preferences and other factors not adequately controlled for that affect both reproduction and IBD risks.

Within each of these types of pathways, some mechanisms may contribute positively to the relationship and others negatively, and the magnitude and even direction of each mechanism may depend on the children's age and vary between sexes and types of IBD. One possible positive contribution could be less exercise (15,16) among parents than childless people. There is also evidence suggesting that obesity, a related factor possibly affecting IBD risks (17), is positively associated with childbearing (18), although another study showed that in women, obesity was particularly common among the childless (19). The results suggest that this or other positive contributions are stronger among men than women, or that they are counteracted by opposing mechanisms among women. When it comes to the relationship between having young (not older) children and CD (not UC) among women, the negative contributions must even be dominating.

The negative contributions to the relationship between childbearing and IBD, which are particularly important for women with young children and with respect to CD, may involve social effects or confounding. For example, one might expect that childless women use or have used oral contraceptives to larger extent than mothers. Our data did not allow control for contraception, but frequency tabulations based on other data with information about medication purchases and childbearing confirmed our expectation (see Web Appendix 4). This difference in contraceptive use may explain a considerable part of the observed pattern if it is the case, as concluded in an American study, that current use of contraceptive pills increases the CD risk very strongly, but has no impact on the UC risk (4). However, other studies have shown modest associations with oral contraception, for both types of IBD (6). This is further explained in Web Appendix 4.

Furthermore, studies have shown that having (young) or expecting children decreases the probability of beginning to smoke and increases the probability of quitting, especially among women (20). Because smoking also has been reported to have adverse impact

especially or exclusively on CD (21), it may in principle contribute to the particularly lus ow CD risk among women with a quite recent birth, although this contribution is probably small given how generally uncommon smoking now is. (10 percent of Norwegian women aged 16-44 smoked during the study period (22)). See elaboration of this argument, based on estimates of smoking differences from the CONOR health surveys, in Web Appendix 4. Unfortunately, the data did not allow us to control for smoking in our models.

Also biological factors may contribute negatively to the relationship between having young children and CD in women. Studies have indicated that, during pregnancy, hormone-driven immunological changes may reduce the severity of diseases caused by inflammation (23). It is possible that these changes also contribute to reducing the *incidence* of such diseases, for some time after pregnancy. Furthermore, the higher levels of sex hormones during pregnancy may have implications for gut motility and other aspects of the gut function (9,24,25), as well as for the composition of gut microbiota (26) and the colonic epithelium (27). The latter may in particular involve the barrier permeability (28,29). However, we are not aware of any studies indicating that these mechanisms are more relevant for CD than UC.

In a Danish study of several autoimmune diseases (10), no associations between parenthood and CD or UC risks were found, but the point estimates were more suggestive of low risk of CD than low risk of UC among parents. The authors used a method quite similar to ours and had access to hospital data for a longer period, 1982-2008, reducing the probability of misclassifying prevalent cases as incident cases (see discussion below). However, they considered the entire age group 15-73, did not group the parents by time since last birth, and did not control for other social variables than marital status. When we estimated a similar model, i.e. for age 18-81 and with control only for age, period and marital status, the

association between motherhood and the CD risk was not significant (OR 0.97, Table 5), but for fathers and mothers the UC risk was elevated (ORs 1.19 and 1.08, respectively, Table 5).

Researchers using the American Nurses' Health Study reported weak indications of low CD and UC risks among mothers compared to childless women (4). A long observation period was used, which reduced the chance of misclassifying prevalent cases as incident, but there were only 700 IBD cases, a broad age group 25-85 was considered, and there were no controls for marital status or socio-economic factors (but for smoking, oral contraceptive use and some health or health-behaviour indicators, which mattered little).

Some studies have shown a reduced chance of relapse of UC and CD some years after pregnancy (30,31), while the evidence for this is less clear in other research (8). Such a pattern accords with what we have observed and may reflect similar biological or social pathways, more aggressive treatment during pregnancy, or confounding.

Limitations

A potential concern in almost all register-based IBD studies is misclassification of prevalent cases as incident. We defined incident cases as at least two IBD hospital contacts after no such contacts in previous years back to 2008, and having lived at least three years in the country, but these cases may include prevalent cases diagnosed before 2008. In principle, an implication of this is that the estimated association between motherhood and the CD risk may be partly a result of a lower probability of becoming mothers among women who already have CD. However, this is probably a small problem in practice because CD (and UC) is not significantly associated with first-birth probabilities, according to supplementary estimation of hazard models for fertility, which means that motherhood actually may reduce the CD risk *even more* than suggested by our estimates, and regardless of how many of the cases that are

actually prevalent (see details in Web Appendix 5). Furthermore, even if the probability of being a mother by a certain age had been clearly lower among those with an earlier CD diagnosis than among disease-free women, the overestimation of the association between motherhood and CD would have been moderate because it is possible that the proportion of cases that are actually prevalent cases is not higher than 20 percent (see Web Appendix 5). It is also important to note that, if the requirement about years of residence in the country was extended from three to five years, which reduces the proportion of cases that may actually be prevalent, the association between motherhood and the CD risk was not weakened (Table 5). One might suspect particularly long periods without hospital contact among immigrants with IBD (and a few unregistered births also among immigrants), but leaving them out did not affect the results (Table 5).

A related issue is that some individuals may have had symptoms before they are diagnosed with IBD, with implications for childbearing. However, when a diagnosed IBD appears to have no impact on first-birth probabilities, it is hard to believe that symptoms from *undiagnosed* IBD can be an important confounder. Additionally, earlier Norwegian studies have indicated that it is uncommon to have severe symptoms for a long time before diagnosis (32,33).

Also the association between education and the IBD risks may, in principle, reflect reverse causality, but as discussed in Web Appendix 6, one should not be concerned about that.

It can in some cases be difficult for a physician to decide between a CD and UC diagnosis, but we think it is reasonable to assume that the diagnosis reported for the last IBD hospital contact is the most correct (34). In any case, it turned out to be unimportant for the conclusion whether the diagnosis reported for the first hospital contact or that reported for the last was used as the diagnosis (See Web Appendix 2).

Finally, it is possible in theory that there are social effects not only on the risk of developing IBD, but also on the chance that IBD is actually diagnosed. However, women with young children have probably had relatively much contact with health personnel during recent years. Thus, unless their gut symptoms are masked by other health problems at this stage (so they do not mention them or the doctor sets an incomplete diagnosis), one would expect a high rather than low chance of diagnosis – of both CD and UC – for this group.

Conclusion

A variety of opposing mechanisms may be responsible for the observed patterns. On the one hand, certain lifestyle changes resulting from parenthood – or uncontrolled determinants of parenthood – may have adverse effects on CD and UC risks (perhaps varying in strength between the sexes and with the children's age). On the other hand, there are also factors that contribute negatively to the relationship between parenthood and IBD, and which appear to be particularly strong for women with young children, and with respect to CD. A beneficial biological effect of pregnancy that operates in the short term is one possible such opposing mechanism. Another possibility is that this group of women use relatively little oral contraception, which may protect against CD, but perhaps not UC. In other words, if the low CD risk among mothers with young children is not a result of hormonal or other biological processes triggered by the pregnancy, it might be the result of another type of mechanism involving sex hormones. However, although an American study supports the idea that the latter may be an important contribution, others have shown no or weak associations between contraceptive pills and IBD risks, and less difference between CD and UC.

ETHICAL ISSUES

The use of register data for the purpose of this study has been approved by the Regional Committees for Medical and Health Research Ethics and the data owners.

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Table 1. Effects of Parenthood and Other Variables on the Odds of Being Diagnosed With IBD, in Discrete-time Hazard Models Estimated for the Years 2011-2016 for Women and Men Older Than 18 Years of Age and Born After 1935.[a]

Characteristics	**Women**			**Men**		
	No. of diagnoses	**OR**	**95% CI**	**No. of diagnoses**	**OR**	**95% CI**
Crohn's Disease						
Number of children						
0	829	1.00	Referent	843	1.00	Referent
≥1	1,491	0.86	0.76, 0.98	1,141	1.01	0.88, 1.15
Marital status						
Never- married	1,082	1.13	1.00, 1.28	1,018	1,06	0.93, 1.21
Married	867	1.00	Referent	768	1.00	Referent
Widowed	73	0.90	0.70, 1.16	16	0.80	0.48, 1.31
Divorced/separated	298	1.13	0.99, 1.29	182	0.96	0.82, 1.13
Education						
Primary[b]	682	1.00	Referent	589	1.00	Referent
Lower secondary	291	0.93	0.80, 1.08	194	1.10	0.92, 1.31
Completed secondary	681	0.89	0.79, 0.99	711	0.91	0.81, 1.02
Lower tertiary	569	0.73	0.64, 0.83	349	0.89	0.77, 1.03
Higher tertiary	97	0.53	0.42, 0.67	141	0.78	0.64, 0.96
Region of residence						
East	1,144	1.00	Referent	996	1.00	Referent
South (Agder-Rogaland)	293	0.89	0.78, 1.01	251	0.85	0.74, 0.97
West	405	1.03	0.92, 1.16	367	1.05	0.93, 1.18
Central	184	0.90	0.77, 1.05	150	0.83	0.70, 0.99
North	294	1.30	1.15, 1.48	220	1.10	0.95, 1.27
Whether municipality of residence is city						
City	1,104	1.00	Referent	981	1.00	Referent
Not city	1,216	1.05	0.96, 1.15	1,003	0.98	0.89, 1.07
Country of birth						
Norway	2,162	1.00	Referent	1,805	1.00	Referent
Other Europe	89	0.57	0.45, 0.73	88	0.63	0.48, 0.81
Other regions	69	0.40	0.30, 0.52	91	0.77	0.60, 0.99
Mother's education						
Primary[c]	1,113	1.00	Referent	938	1.00	Referent
Lower secondary	519	0.97	0.84, 1.14	466	0.93	0.83, 1.06
Completed secondary	343	1.10	0.96, 1.27	256	0.90	0.77, 1.06
Lower tertiary	306	0.98	0.84, 1.14	284	0.92	0.78, 1.08
Higher tertiary	39	0.90	0.63, 1.27	40	0.82	0.58, 1.16
Father's education						
Primary[c]	1,065	1.00	Referent	857	1.00	Referent
Lower secondary	457	0.98	0.86, 1.10	392	0.97	0.85, 1.11
Completed secondary	413	0.93	0.82, 1.06	355	0.98	0.86, 1.13
Lower tertiary	289	0.87	0.75, 1.02	266	0.96	0.82, 1.13
Higher tertiary	96	0.75	0.59, 0.94	114	1.00	0.79, 1.25
Mother's or father's						
education unknown						
No	1,905	1.00	Referent	1,684	1.00	Referent
Yes	415	1.07	0.91, 1.26	300	0.92	0.77, 1.10
Total number of diagnoses	2,320			1,984		
Total exposure time (one-year observations)	10,530,937			10,757,656		
Number of individuals contributing exposure time	1,909,840			1,974,385		
Ulcerative Colitis						
Number of children						
0	1,190	1.00	Referent	1,656	1.00	Referent
≥1	2,923	1.01	0.91, 1.11	3,097	1.11	1.02, 1.21

Marital status						
Never- married	1,647	1.02	0.93, 1.11	2,038	0.88	0.81, 0.96
Married	1,778	1.00	Referent	2,201	1.00	Referent
Widowed	152	0.96	0.80, 1.14	55	0.92	0.70, 1.20
Divorced/separated	536	1.03	0.94, 1.14	459	0.87	0.78, 0.96
Education						
Primary[b]	995	1.00	Referent	1,134	1.00	Referent
Lower secondary	539	1.00	0.90, 1.12	502	1.11	0.99, 1.24
Completed secondary	1,126	1.01	0.92, 1.10	1,919	1.18	1.09, 1.28
Lower tertiary	1,192	0.95	0.87, 1.05	874	1.04	0.94, 1.14
Higher tertiary	261	0.83	0.72, 0.97	324	0.81	0.70, 0.92
Region of residence						
East	1,905	1.00	Referent	2,207	1.00	Referent
South (Agder-Rogaland)	579	1.06	0.97, 1.17	735	1.09	1.00, 1.19
West	722	1.12	1.03, 1.22	879	1.11	1.02, 1.20
Central	421	1.26	1.13, 1.40	424	1.05	0.94, 1.16
North	486	1.33	1.21, 1.48	508	1.15	1.04, 1.27
Whether municipality of residence is city						
City	2,000	1.00	Referent	2,343	1	Referent
Not city	2,113	1.04	0.98, 1.11	2,410	0.96	0.91, 1.02
Country of birth						
Norway	3,814	1.00	Referent	4,386	1.00	Referent
Other Europe	172	0.70	0.59, 0.84	206	0.63	0.53, 0.74
Other regions	127	0.49	0.40, 0.60	161	0.61	0.51, 0.73
Mother's education						
Primary[c]	1,980	1.00	Referent	2,337	1.00	Referent
Lower secondary	972	0.96	0.89, 1.05	1,157	0.92	0.85, 0.99
Completed secondary	494	0.99	0.88, 1.10	575	0.95	0.86, 1.05
Lower tertiary	580	1.04	0.92, 1.16	595	0.90	0.81, 1.01
Higher tertiary	87	1.11	0.87, 1.40	89	0.94	0.75, 1.19
Father's education						
Primary[c] (ref)	1,847	1.00	Referent	2,081	1.00	Referent
Lower secondary	800	0.95	0.87, 1.04	999	1.02	0.94, 1.11
Completed secondary	663	0.95	0.86, 1.05	844	1.08	0.99, 1.18
Lower tertiary	579	1.05	0.94, 1.18	585	0.99	0.89, 1.10
Higher tertiary	224	0.95	0.81, 1.12	244	0.99	0.85, 1.16
Mother's or father's						
education unknown						
No	3,378	1.00	Referent	3,993	1.00	Referent
Yes	735	0.92	0.81, 1.03	760	0.95	0.85, 1.06
Total number of diagnoses	4,113			4,753		
Total exposure time (one-year observations)	10,530,937			10,757,656		
Number of individuals contributing exposure time	1,909,840			1,974,385		

Abbreviations: CI, confidence interval; OR, odds ratio

[a] It was also controlled for age (in two-year categories) and calendar year (in one-year categories). Effects of age (in broader categories) and year are shown in Appendix 1. Note that we got almost the same estimates if we instead used a multinomial regression model where 'neither CD nor UC' was the reference outcome category and CD and UC were the two other outcome categories.

[b] Including 1% unknown, most of them born abroad. Excluding this group had almost no impact on estimates

[c] Including unknown, but because also a dummy variable for unknown was included, effect estimates are based on comparisons among those for whom parental education was known.

Table 2. Age-specific Effects of Parenthood on the Odds of Being Diagnosed With IBD, in Discrete-time Hazard Models Estimated for the Years 2011-2016 for Women and Men Older Than 18 Years of age and Born After 1935.[a]

No. of Children	Age 18–44 Years						Age 45–81 Years					
	Women			Men			Women			Men		
	No. of Diagnoses	OR	95% CI	No. of Diagnoses	OR	95% CI	No. of Diagnoses	OR	95% CI	No. of Diagnoses	OR	95% CI
Crohn's disease												
0	720	1.00	Referent	698	1.00	Referent	109	1.00	Referent	145	1.00	Referent
≥1	555	0.79	0.67, 0.93	383	0.97	0.82, 1.15	936	1.03	0.82, 1.28	758	1.04	0.84, 1.27
Ulcerative colitis												
0	1,019	1.00	Referent	1,329	1.00	Referent	171	1.00	Referent	327	1.00	Referent
≥1	1,106	0.97	0.86, 1.09	993	1.14	1.02, 1.27	1,817	1.14	0.96, 1.36	2,104	1.09	0.95, 1.25

Abbreviations: CI, confidence interval; OR, odds ratio

[a] It was also controlled for age, calendar year, marital status, education, region of residence, whether municipality of residence was a city, country of birth, mother's education, father's education, and whether parents' education was known.

Table 3. Effects of Parenthood and Time Since Last Birth on the Odds of Being Diagnosed With IBD, in Discrete-time Hazard Models Estimated for the Years 2011-2016 for Women and Men Older Than 18 Years of Age and Born After 1935.[a]

No. of Children and Time Since Last Birth, years	Women			Men		
	No. of Diagnoses	OR	95% CI	No. of Diagnoses	OR	95% CI
Crohn's Disease						
0	829	1.00	Referent	843	1.00	Referent
≥1 0- 4	219	0.73	0.62, 0.86	219	0.97	0.82, 1.15
5- 9	202	0.87	0.72, 1.05	165	0.97	0.79, 1.10
10-14	174	0.87	0.71, 1.07	131	0.88	0.71, 1.10
15-19	165	0.89	0.72, 1.10	131	0.95	0.76, 1.19
≥20	731	1.08	0.89, 1.31	485	1.22	1.01, 1.49
Ulcerative Colitis						
0	1,190	1.00	Referent	1,656	1.00	Referent
≥1 0- 4	487	0.95	0.84, 1.07	580	1.14	1.02, 1.27
5- 9	369	0.94	0.82, 1.08	405	1.05	0.92, 1.19
10-14	338	1.02	0.88, 1.18	353	1.06	0.92, 1.21
15-19	334	1.08	0.92, 1.26	354	1.09	0.94, 1.25
≥20	1,395	1.12	0.98, 1.30	1,405	1.15	1.02, 1.30

Abbreviations: CI, confidence interval; OR, odds ratio

[a] It was also controlled for age, calendar year, marital status, education, region of residence, whether municipality of residence was a city, country of birth, mother's education, father's education, and whether parents' education was known .

Table 4. Effects of a Variable Combining Number of Children and Time Since Last Birth on the Odds of Being Diagnosed With IBD, in Discrete-time Hazard Models Estimated for the Years 2011-2016 for Women and Men Older Than 18 years of Age and Born After 1935.[a]

Sex and No. of Children	Time Since Last Birth, years					
	0–19, or childless			≥20		
	No. of Diagnoses	OR	95% CI	No. of Diagnoses	OR	95% CI
Crohn's Disease						
Women						
0	829	1.00	Referent			
1	192	0.81	0.68, 096	127	1.05	0.84, 1.32
2	349	0.84	0.71, 0.98	334	0.99	0.81, 1.21
3	162	0.74	0.60, 0.90	183	0.98	0.78, 1.22
≥4	57	0.78	0.58, 1.04	87	1.22	0.92, 1.61
Men						
0	843	1.00	Referent			
1	180	0.97	0.82, 1.16	97	1.35	1.05, 1.73
2	276	0.96	0.81, 1.14	221	1.12	0.90, 1.39
3	143	0.93	0.75, 1.15	139	1.30	1.01, 1.66
≥4	47	0.76	0.55, 1.05	38	0.97	0.67, 1.40
Ulcerative Colitis						
Women						
0	1190	1.00	Referent			
1	381	1.00	0.88, 1.14	225	1.08	0.91, 1.29
2	669	0.97	0.86, 1.09	646	1.06	0.92, 1.23
3	367	0.99	0.86, 1.14	386	1.10	0.93, 1.30
≥4	111	0.92	0.74, 1.14	138	1.02	0.82, 1.27
Men						
0	1656	1.00	Referent			
1	474	1.18	1.06, 1.32	198	1.02	0.86, 1.22
2	684	1.05	0.94, 1.17	687	1.18	1.03, 1.35
3	391	1.08	0.95, 1.23	382	1.16	1.00, 1.35
≥4	143	0.98	0.81, 1.18	138	1.15	0.93, 1.41

Abbreviations: CI, confidence interval; OR, odds ratio

[a] It was also controlled for age, calendar year, marital status, education, region of residence, whether municipality of residence was a city, country of birth, mother's education, father's education, and whether parents' education was known.

Table 5. Effects of Parenthood on the Odds of Being Diagnosed With IBD, Under Various Alternative Specifications.

Model Specification	**OR**	**95% CI**
Crohn's disease in women aged 18-44		
Model as in Table 2	0.79	0.67, 0.93
Same except marital status not included in the model	0.77	0.66, 0.90
Same except those born abroad excluded	0.79	0.67, 0.94
Same except conditioned on five years of residence	0.77	0.64, 0.93
Same except considered as case also if there was only one IBD hospital contact, but the woman had not lived three years in the country up to 2016	0.79	0.68, 0.91
Same except considered as case also if there was only one IBD hospital contact, regardless of years of residence up to 2016	0.82	0.71, 0.93
Same except considered as case only if both first and last IBD hospital contact included CD diagnosis	0.76	0.64, 0.90
Same except considered as case if first IBD hospital contact included CD diagnosis, regardless of last diagnosis	0.75	0.64, 0.88
Crohn's disease in women aged 18-81		
Model as in Table 1	0.86	0.76, 0.98
Same except only age, period and marital status included in the model	0.97	0.86, 1.10
Ulcerative colitis in men aged 18-81		
Model as in Table 1	1.01	0.91, 1.11
Same except only age, period and marital status included in the model	1.08	0.99, 1.19
Ulcerative colitis in men aged 18-81		
Model as in Table 1	1.11	1.02, 1.21
Same except only age, period and marital status included in the model	1.18	1.10, 1.30

Abbreviations: CI, confidence interval; OR, odds ratio