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

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ONLINE SUPPLEMENTARY MATERIAL

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Web Appendix 1: Effects of control variables

According to models estimated for the entire age group (Table 1), the CD risk was relatively low for both sexes in southern compared to eastern Norway (although the difference was significant only at the 10% level for women), among foreign born, and among better-educated individuals. Among women, high paternal education was associated with low risk, while living in the north was associated with high risk. Among men, the risk was relatively low in central Norway. A low risk among foreign born and better educated and a high risk in the north appeared in the models for UC as well (and the latter then for both sexes), but there were also some distinct patterns in the UC risk: Among men, there was an inversely U-shaped association with education, while maternal education above the compulsory level was associated with low risk. Furthermore, the UC risk was raised in southern, western or central Norway for at least one of the sexes, and for men it was relatively high among the married compared to the divorced or never-married (while there were indications in the opposite direction in the models for CD in women).

These association between various control variables and IBD risks accord well with existing literature. For example, a north-south gradient has appeared in several studies (1,2), and although some early investigations indicated that high socioeconomic status may increase the IBD risk or at least not reduce it (3,4), a recent Swedish analysis showed a clearly reduced risk of CD (but not UC) among women and men with tertiary education (5). In our analysis, there was also evidence of a relatively low UC risk among the better educated, but that pattern was less clear than for CD, which may partly reflect that smoking – which is strongly associated with education (6) - may increase the CD risk while having weaker or even opposite effect on UC (7). Furthermore, some investigations have shown low risks among immigrants from developing countries (8).

Less interestingly, the IBD risks are as expected lower for the oldest in our study population (Web Table 1). They also appear to decrease over the study period, probably as a result of the statistical design: Our definition of an ‘incident case’ or ‘diagnosis’ involves a requirement about having had at least two IBD hospital contacts by the end of the study period, which is less likely when the first such contact occurs in one of the last years. Additionally, in the first years of the study period there is probably a particularly large number of ‘prevalent cases’ (which we ideally would have preferred to keep out of the analysis) that add to the true incident cases, and that are included among what we reckon as incident cases.

Web Table 1. Effects of Age and Year 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]

Crohn's disease	*Women*			*Men*		
	Number of diagnoses	OR	95% CI	Number of diagnoses	OR	95% CI
Age						
18-29	664	1.12	0.97, 1.30	526	1.07	0.92, 1.24
30-39 (ref)	388	1		374	1	
40-49	463	1.00	0.87, 1.15	391	0.90	0.77, 1.04
50-59	340	0.76	0.65, 0.90	339	0.85	0.72, 0.99
60-69	327	0.77	0.64, 0.92	243	0.69	0.57, 0.83
70-81	138	0.52	0.41, 0.66	111	0.61	0.47, 0.83
Period						
2011 (ref)	459	1		398	1	
2012	429	0.93	0.81, 1.06	350	0.87	0.75, 1.00
2013	406	0.87	0.76, 0.99	325	0.79	0.69, 0.92
2014	359	0.76	0.66, 0.87	341	0.82	0.71, 0.95
2015	374	0.78	0.68, 0.89	307	0.73	0.62, 0.84
2016	293	0.60	0.51, 0.69	263	0.61	0.52, 0.71
Ulcerative colitis	*Women*			*Men*		
	Number of diagnoses	OR	95% CI	Number of diagnoses	OR	95% CI
Age						
18-29	915	0.96	0.86, 1.08	996	0.90	0.89, 1.10)
30-39 (ref)	766	1		868	1	
40-49	817	0.90	0.82, 1.00	922	0.86	0.78, 0.95
50-59	736	0.88	0.79, 0.99	895	0.91	0.82, 1.01
60-69	575	0.78	0.68, 0.89	755	0.86	0.77, 0.97
70-81	304	0.73	0.61, 0.87	317	0.70	0.60, 0.82
Period						
2011 (ref)	902	1		1,049	1	
2012	737	0.80	0.73, 0.89	810	0.76	0.69, 0.83
2013	726	0.78	0.71, 0.86	826	0.76	0.70, 0.84
2014	675	0.71	0.64, 0.79	736	0.67	0.61, 0.74
2015	625	0.65	0.59, 0.72	801	0.72	0.66, 0.79
2016	448	0.46	0.95, 1.16	531	0.47	0.42, 0.52

Abbreviations: CI, confidence interval; OR, odds ratio

[a] The model was as in Table 1 except for broader age categories.

Web Appendix 2: Alternative definitions of the outcome variable

Even if an IBD hospital contact during the year in focus was not followed by another one up to 2016, so it was not counted as a case in our analysis, the person may actually have IBD. In supplementary analysis, we included these single IBD contacts as cases if the individual had not lived three full years in Norway afterwards, because a later contact (as an indication of

disease) would then be particularly likely. We found, for example, that the association between motherhood on the CD risk at age 18-44 remained unchanged at 0.79 (Table 5). When we included the single IBD contacts as cases also if the individual had lived in the country for *more* than three years, the association weakened only slightly to 0.82.

Furthermore, when we included among the CD cases only the cases where CD was registered both at the first and last IBD hospital contact, the relationship with motherhood at age 18-44 was weaker (0.76) than originally estimated. It was weaker (0.75) also if we defined CD cases according to the first rather than last IBD diagnosis.

Web Appendix 3: Potential over-controlling

When the intention is to assess the importance of parenthood for the IBD risk, one should ideally control for determinants of childbearing that also may affect the IBD risk. Some of the control variables that we included, in addition to age and calendar year, were time-varying: own education, region of residence, whether the municipality of residence was a city, and marital status (because a more appropriate indicator of actual living arrangements was not available). These variables referred, like the fertility variable, to the situation at the start of the one-year observation intervals, and this situation may to some extent have been *affected* by earlier childbearing. In that case, we would be tapping out part of a possible social effect of parenthood on IBD. One might expect that especially the inclusion of marital status could be problematic from this perspective, but supplementary estimation suggested that it is not a strong confounder and presumably even less important as a mediator: When marital status was not included in the model for CD among women of age 18-44, the odds ratio associated with motherhood was 0.77 (rather than 0.79 in the full model; Table 5).

Web Appendix 4: Oral contraceptive use and smoking as confounders or mediators

In this discussion of the possible importance of oral contraceptive use and smoking as confounders or mediators, we focus for simplicity on the analysis of individuals aged 18-44, which showed, for example, that the risk of CD was 21% lower for mothers than childless women, net of various control variables. (The odds ratio, which is essentially the same as the risk ratio, was 0.79.)

Studies of how use of oral contraceptive pills affects the IBD risk have given very different results. Some have indicated an adverse effect, while others have not shown any significant association, or that the association varies with other factors. For example, a recent meta-analysis showed that current use of oral contraception increased the CD risk by 24% compared to never-users (risk ratio 1.24), while the corresponding risk ratio for UC was 1.30 (9). In contrast, a study from the US which included about 700 IBD cases, and which could not be included in the mentioned meta-analysis, showed a risk ratio of 2.8 for CD, while there was no significant association with UC except among smokers (10). If it instead had been compared with all those not currently using oral contraception (i.e., either former users or

never users), the risk ratio for CD would probably have been close to 2. Adjustment for a few demographic factors and health and health-behaviour indicators had modest impact. Another study not included in the review did not show significant association between pill use and any of the two main types of IBD. This analysis was based on data from the Asia-Pacific region and included about 350 IBD cases. (11)

We used some numbers calculated from a file with information from the Norwegian Prescription Database (12) and the Population Register to get an impression of how much current use of contraceptive pills may contribute to the differences in IBD risks we observe between childless women and mothers at age 18-44 in our study period. In 2010, the probability of currently using contraceptive pills was 13 percentage points higher among childless 30-year old women than among mothers of the same age (unpublished calculations by Vidar Hjellvik, Norwegian Institute of Public Health). The corresponding differences at ages 20, 25, 35, 40 and 44 years were 33, 23, 6, 3 and 2 percentage points, respectively. The average of these six numbers is 13 percentages points. The corresponding average for 2015 was 14 percentage points. Note that it is impossible with these data, which only go back to 2004, to calculate the proportion who are former pill users.

If current use of the pill increases the chance of CD by 24% (as reported in the mentioned meta-analysis (9), admittedly based on comparisons with never-users), and if there is a 14 percentage points larger chance of using pills among the childless than the mothers (for example 24% current users among the childless and 10% among mothers, as observed at age 30 in 2015), this alone would lead to a CD risk ratio of $(1+0.24\cdot0.10)/(1+0.24\cdot0.24)=0.97$. To spell this out in more detail, the CD risk among mothers would be, say, r for those who are not current pill users and $r\cdot1.24$ for the current users. The average, given that 10% are users, would then be $r(0.90+1.24\cdot0.10)=r(1+0.24\cdot0.10)$. Similarly, the CD risk among the childless would be $r(1+0.24\cdot0.24)$, assuming that nothing else matters for the risk (if it did, another factor than r would have to be used for the childless). In other words, it seems that differences in current use of oral contraception can explain little of the observed risk ratio of 0.79 (obtained with several control variables included).

Obviously, if the effect of current pill use (relative to those not currently using the pill) instead is as strong as 2, which was indicated by the American study, much more would be explained; the risk ratio stemming from a pill effect exclusively would be $(1+1\cdot0.10)/(1+1\cdot0.24)=0.89$. Also, the fact that we see no relationship between motherhood and UC would be consistent with the lack of a pill effect on UC according to that study. However, one should keep in mind that no other study has shown so strong effects on CD. In fact, in other studies based on more than 100 cases the point estimates of the effect have been between 0.7 and 1.4 (9).

In these calculations, the distinction has been between those who currently use the pill and those who do not (former users or never-users). It is likely that, although the current pill use is lower among mothers than childless in the age group that we consider, many of the mothers may have used pills earlier, and to a larger extent than the childless who are not current users. Because former use of oral contraception has also been reported to increase the

risk of CD (and perhaps also UC) (10,13), we would probably have estimated higher risk ratios than 0.97 and 0.89 (i.e. closer to 1) if we had been able to take former use into account.

Similarly, one may get an impression of the contribution from smoking by using evidence from earlier studies about the relationship between smoking and IBD risks and information from health surveys (possibly in combination with register data) about differences in smoking between childless and parents. Our data files included information on smoking from the CONOR surveys (14) for a small proportion of the individuals. The surveys covered the years 1995-2003, when the proportion smokers in the age group 16-44 was more than twice as high as in our study period (according to Statistics Norway's databank https://www.ssb.no/statbank/table/05307/). We calculated the difference in the proportion current smokers between childless and parents in the age groups 20-24, 25-29, 30-34, 35-39 and 40-44. The average across these age groups was 2 percentage points among women and 0 among men. When we instead estimated a linear probability model for the chance of currently smoking, and controlled for age, we found a difference of 4 percentage points for women and 2 for men. The differences with respect to past smoking were 1-2 percentage points for both sexes.

If we assume that the CD risk ratio associated with current smoking is 1.8, as concluded in a meta-study (7) where it was compared with never-smokers, and if we assume that the difference in current smoking between childless women and mothers is 4 percentage points (probably at the high end because smoking was generally less common in the study period than more than a decade earlier) – say 12% among the childless and 8% among mothers - smoking differences alone would cause a CD risk ratio of $(1+0.8\cdot0.08)/(1+0.8\cdot0.12)=0.97$ between mothers and childless women. Adding an effect of former smoking, which is also slightly more common among the childless, would obviously have little impact. Conversely, differences in current smoking between childless women and mothers would contribute to a UC risk ratio slightly larger than 1 (i.e. pointing in the opposite direction) if we assume a protective effect such as reported (7), although this would be counteracted by the pattern in former smoking, which has been reported to have adverse effect on UC.

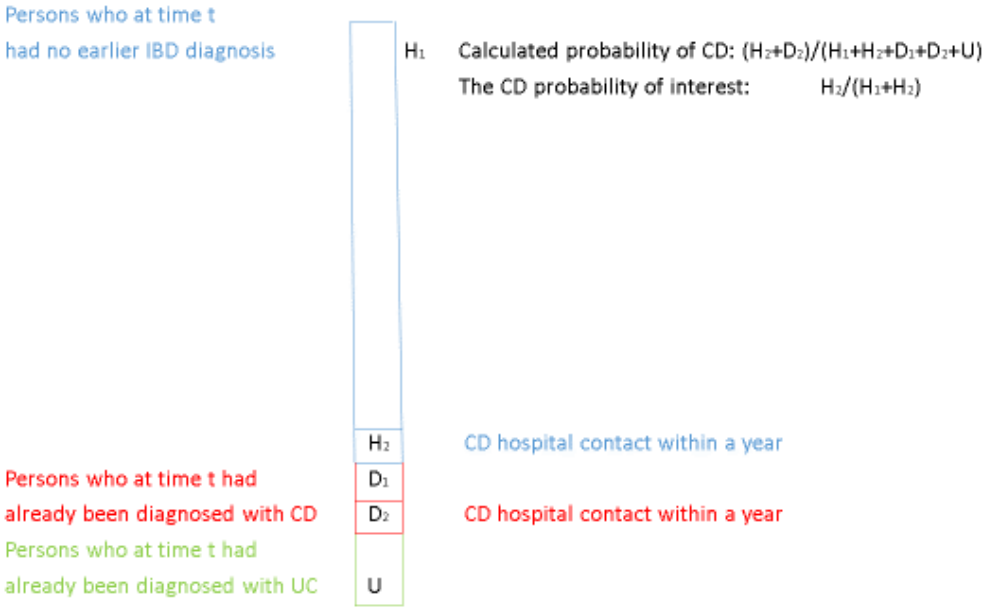
Web Appendix 5: The potential reverse causality problem arising because some incident cases may actually be prevalent cases – with special attention to CD in women aged 18-44

Further specification of the problem

The persons we assume to be disease-free at the beginning of year *t* (because they have not had any IBD hospital contacts since 2008 and have lived at least three years in the country) can be considered as consisting of four groups: Among those actually not diagnosed with IBD, a small subgroup of H_2 persons have an IBD hospital contact within the year and at least one more afterwards, the last being registered with a CD diagnosis (see Web Figure 1). The remaining H_1 do not receive such a CD diagnosis. The third and fourth groups, which are also small, consist of persons who have actually been diagnosed with CD earlier. The D_2 persons

in the third group have an IBD hospital contact within the year and at least one more afterwards, the last being registered with a CD diagnosis (i.e. they show up in a hospital again after a period of at least three years). The D_1 persons in the fourth group do not have an IBD hospital contact in year *t* followed by another later. A small fifth group consists of U persons who have been diagnosed with UC earlier, and who may or may not have an IBD hospital contact within the year. It is not important in the argument that follows to make a distinction between these two subgroups of those with an earlier UC diagnosis. (Note that this definition of five groups is based on the idea that, if what we consider an incident CD case has actually been diagnosed earlier, that diagnosis is also CD - in line with our decision to define the IBD type according to the diagnosis registered at the last IBD hospital contact.)

Web Figure 1. The Population Groups Included in the Argumentation.



The goal of our analysis is to learn about variations in the one-year probability that a disease-free individual receives a diagnosis within a year. Lacking complete information about the situation, we essentially consider this probability as $(H_2+D_2)/P$, where P is the entire population $H_1+H_2+D_1+D_2+U$ that we assume to be disease-free, while the probability we are actually interested in is $H_2/(H_1+H_2)$. The latter is approximately the same as H_2/P because D_1, D_2 and U are small.

Given our interest in the difference between childless women and mothers, a potential problem arises if there are relatively many manifestations of prevalent cases (D_2) compared to incident cases (H_2), and the difference in D_2/P between childless women and mothers is markedly different from the difference in H_2/P between childless women and mothers. The difference in D_2/P between childless women and mothers reflects effects of motherhood on disease risks before the age the person has attained at time *t*, but is also a result of diseases

affecting childbearing before *t:* If those with CD are less likely than the disease-free to become parents, it will contribute to making $(D_2+D_1)/P$ higher among the childless, and hence probably also D_2/P. The implication is, for example, that even if the probability H_2/P (which is close to the $H_2/(H_1+H_2)$ that we ideally want to estimate) does not vary between childless and mothers, the one that we measure, $(H_2+D_2)/P$, may do.

The proportion prevalent cases

To get an idea about how many of our apparently incident cases that may actually be prevalent cases, we first checked how common it is to have intervals of more than three years between IBD hospital contacts. For simplicity, we considered only one group of individuals – those who were 18-44 years old in 2008, had lived in Norway at the beginning of each of the years 2008-2016, had no IBD hospital contacts in 2012-2014, had either at least two contacts in 2015 or one in 2015 and at least one in 2016, and whose last IBD hospital contact was registered with CD. Within this group, 24% had at least one IBD hospital contact in the earlier years 2008-2011. This should be reckoned as a CD case given our definition of IBD type, and since the last IBD hospital contact within the 2015-2016 period was registered with a CD diagnosis. Among two-thirds of these individuals, this earlier IBD hospital contact – from now called CD hospital contact – took place within the last two of these years (2010-2011). If we instead consider those who had a five-year period (2010-2014) without IBD hospital contact, 9% had CD hospital contact the previous two years (2008-2009).

To the extent that we can generalize from these numbers to earlier years, 24% of the CD cases we have identified in 2011 may actually be prevalent cases (CD hospitals contacts before 2008). Among the cases in 2013-2016, the corresponding number may be around 9% or even lower, because although we have a three-year residence requirement, many have lived longer in the country, and even more than five years. This means that, as an average over the years 2011-2016, around 15-20% of the apparently incident cases in our analysis may be prevalent cases. Similarly, in our supplementary analyses with a five-year residence restriction, the proportion of the cases that are actually prevalent cases may be lower than 9%.

There are no firmly established incidence rates that it is reasonable to compare with to get an alternative indication of the proportion prevalent cases. With our definition of incident cases, we have a CD incidence rate of 20/100000 in the age group 18-81 over the years 2011-2016, for both sexes combined, while the UC incidence rate is 42/100000. (This was calculated from cases and exposure times reported in Table 1.) Taking into account that this age group constitutes only 74% of the Norwegian population, while it – according to unpublished results from an ongoing clinical study - includes 80% of the cases, we would get CD and UC incidence rates of 19/100000 and 40/100000 for the whole population. These numbers are higher than most others from rich countries, but lower than the top levels: CD incidence estimates from relatively recent years vary strongly and range from 0 to 29/100000, while the variation in UC incidence estimates is even larger, the lowest being 1/100000 and the highest 58/100000(15).

Fertility models

We estimated discrete-time hazard models for first births in 2010-2015. One-year observation intervals were used and, for simplicity, the analysis was restricted to women who lived in Norway at the beginning of all the years 2008-2016. The start of the follow-up was the year when the person turned 18 or in 2010, whatever occurred last, and the end was at age 44 (as few women have children at higher ages), when the person had become a parent, or in 2015, whatever occurred first (because births in 2016 were not included in the data). The models included two variables that referred to the situation at the beginning of the one-year observation interval: age and a disease indicator for whether the woman had had at least two IBD hospital contacts since 2008. The IBD type was set to CD or UC depending on whether the last IBD contact (within the period 2008-2016) was registered with a CD or UC diagnosis. Place of residence, parents' education and own education were included in supplementary analysis, but this had almost no impact on the effect of IBD on the first-birth probability.

Having CD actually *increased* the odds of having a first birth by 2% (not shown in tables), although this difference was far from significant. The point estimates suggested that the effect of CD was positive at relatively low ages and negative at higher ages. In other words, those with CD became mothers to the same extent, but the estimates indicated that they entered motherhood earlier. According to predictions from a model that included an interaction between age and CD, a woman who is childless at age 18 has a 51% of becoming a mother before age 30 if she has CD in all these years and 48% if she does not have CD. The corresponding proportions at age 40 are 81% and 82%.

In the calculations below, it is for simplicity zoomed in on women aged 30 – which is almost in the middle of the reproductive period - and it is assumed that the probability of being a mother at that age is 50% for those with no earlier IBD diagnosis. The corresponding proportion among those with CD is set to different levels.

In contrast to the very small differences in first-birth rates, the second- and third-birth rates are reduced by about 20% among women (one- and two-child mothers respectively) with CD, according to similar analysis of those parity transitions. However, second and higher-order births are not relevant to consider when the focus – as in this argumentation about potential reverse causality - is on the difference between childless women and all mothers (in the age group 18-44). The potential impact of CD on women's childbearing has only been analysed in a few other studies, based on quite small data sets (16). Two of these studies, covering the 1980s or earlier decades, showed a lower number of children among women with CD. A more recent American study, without a good comparison group, pointed in the same direction and also showed a larger proportion of voluntary childless among women with CD (17). In a larger and more recent study from the UK, a 12% reduced fertility rate was observed among women with CD. This was based on a Poisson regression model that did not distinguish between first and higher-order births (18).

Implications for our estimates of the effect of motherhood on CD

As an illustration of how the combination of CD effects on fertility and misclassification of prevalent cases as incident cases may affect our key estimates, let us consider a group of N women who are 18 years old. Let us also assume that all of them are childless at that age and survive at least until a few years after they turn 30, and (to mimic how women who are 30 contribute in our analysis) that they have no IBD hospital contact during the three years before age 30. Assume further that 0.003% of them already have CD when they are 18, and have another IBD contact the year they are 30 and at least one subsequent contact, the last being registered with a CD diagnosis. The number 0.003% is not critical. A much smaller or larger proportion could have been chosen. It is the ratio between this number and the proportion with a new diagnosis at age 30 (see below) that matters. We could have used symbols instead of numbers, but expect that a less abstract argumentation will be easier to read.

Furthermore, assume that an additional small proportion x have CD at age 18 and do *not* have IBD hospital contact the year they turn 30 and at least one subsequent contact. As further explained below, these women can safely be ignored. Assume also that women without IBD have 50% chance of being mothers when they are 30, while this proportion is 40% among those with CD (as an example, and in contrast to the 3% higher proportion among those with CD that was predicted from the model). For simplicity, assume also that one cannot be diagnosed with IBD between age 18 and age 30, i.e. all cases date back to the ages below 18. As explained below, this assumption is not critical. Finally, assume that a small proportion y have UC at age 18, and that 45% of them have become mothers at age 30, although both those numbers are cancelled out at an early stage in the calculations below.

Then, at age 30, the number of mothers who already have CD is

$$N \cdot (0.00003+x) \cdot 0.40,$$

while the number of childless who have CD is

$$N \cdot (0.00003 +x) \cdot 0.60.$$

Returning to the earlier nomenclature, the D_1 and D_2 values for mothers and childless are

$$D_2^{(\text{mother})} = N \cdot 0.00003 \cdot 0.40,$$

$$D_2^{(\text{childless})} = N \cdot 0.00003 \cdot 0.60,$$

$$D_1^{(\text{mother})} = N \cdot x \cdot 0.40, \text{ and}$$

$$D_1^{(\text{childless})} = N \cdot x \cdot 60.$$

Similarly, the number of mothers who already have UC is

$$U^{(\text{mother})} = N \cdot y \cdot 0.45,$$

while the number of childless who have UC is

$$U^{(\text{childless})} = N \cdot y \cdot 0.55.$$

Obviously, the number of mothers in total is

$$P^{(mother)} = N\cdot(0.00003+x)\cdot 0.40 + N\cdot y\cdot 0.45 + N\cdot(1-0.00003-x-y)\cdot 0.50,$$

where the last term is the number of mothers with no previous IBD diagnosis, (H_1+H_2). Thus, D_2 among the mothers divided by the total number of mothers is

$$D_2^{(mother)}/P^{(mother)} = N\cdot 0.00003\cdot 0.40 /$$

$$(N\cdot(0.00003+x)\cdot 0.40 + N\cdot y\cdot 0.45 + N\cdot(1-0.00003-x-y)\cdot 0.50),$$

and after approximation, given the small numbers 0.00003, x and y,

$$D_2^{(mother)}/P^{(mother)} = 0.00003\cdot 0.40/0.50.$$

The corresponding number among the childless is

$$D_2^{(childless)}/P^{(childless)} = 0.00003\cdot 0.60/0.50.$$

Let us then assume that, among the $N\cdot(1-0.00003-x-y)$ disease-free 30-year olds, 0.009% get a CD diagnosis the next year. Assume further that this proportion is $0.009\%\cdot 0.84/k$ among mothers (who constitute 50%) and $0.009\%\cdot 1/k$ among childless (the remaining 50%), where $k=(1+0.84)\cdot 0.5=0.92$. Thus, the ratio of the proportions is 0.84, which is a convenient "real" effect of motherhood on CD - as will be seen below - and the total number of new CD diagnoses across motherhood status among the disease-free is $N\cdot(1-0.00003-x-y)\cdot 0.00009$, or approximately $N\cdot 0.00009$, so $D_2^{(total)}/(H_2^{(total)}+D_2^{(total)}=1/4$. (The total incidence is 12 per 100000, which is a reasonable number, but as already pointed out, that is not important for the argument.)

In other words, the number of new CD cases among mothers is

$$H_2^{(mothers)} = N\cdot(1-0.00003-x-y)\cdot 0.50\cdot 0.00009\cdot 0.84/k$$

while that among the childless is

$$H_2^{(childless)} = N\cdot(1-0.00003-x-y)\cdot 0.50\cdot 0.00009\cdot 1/k.$$

Thus, the number of CD cases (H_2+D_2) among the mothers relative to the total number of mothers is, after approximation:

$$(D_2^{(mothers)}+H_2^{(mothers)})/P^{(mothers)} = (0.00003\cdot 0.40\cdot k+0.00009\cdot 0.50\cdot 0.84)/(k\cdot 0.50)$$

while the corresponding proportion among the childless is

$$(D_2^{(childless)}+H_2^{(childless)})/P^{(childless)} = (0.00003\cdot 0.60\cdot k+0.00009\cdot 0.50\cdot 1)/(k\cdot 0.50).$$

The ratio of these ratios, which corresponds to the effect one would estimate in an analysis, is

(1) $(0.00003\cdot 0.40\cdot k+0.00009\cdot 0.50\cdot 0.84)/ (0.00003\cdot 0.60\cdot k+0.00009\cdot 0.50\cdot 1).$

This ratio is 0.79, which is precisely the effect we estimated for the age group 18-44. If we assume that we would have estimated the same effect for the women aged 30, we can say that the effect at that age is consistent with i) a real effect of motherhood on CD at that age that is 0.84, ii) one-fourth of the cases being prevalent cases dating back to age 18 or earlier, and iii) these cases reducing the chance of being a mother at age 30 from 50% to 40%. In other words, we have overestimated the effect; it is not really as strong as it seems to us.

This number 0.84 is shown in Web Table 2 along with other real effects of motherhood on CD at age 30 that, under various assumptions about effects of CD on motherhood and proportion prevalent cases, gives an estimated effect of 0.79. Note that, when CD has no effect on motherhood (i.e. also 50% of women with CD have become mothers by age 30), as we have essentially found, we will actually *underestimate* the effect. Mathematically, this is because we would then have the same term ($0.00003 \cdot 0.50 \cdot k$) in the numerator and the denominator of the fraction (1) above, and the fraction will be closer to 1 than in the absence of this term (when the fraction is equal to the real effect of motherhood on CD).

Web Table 2. Real Effects of Having a Child on the CD Risk That Would Lead to a Corresponding Estimated Effect of 0.79, by Proportion Among Those With CD who Have Become Mothers by Age 30 (While the Corresponding Proportion Among Those Without CD is 50%) and Proportion of Apparently Incident Cases That Are Actually Prevalent Cases.[a]

Proportion of those with CD who have become mothers by age 30	Proportion of apparently incident cases that are actually prevalent cases				
	1/3	1/4	1/5	1/6	1/10
50%	0.70	0.73	0.74	0.75	0.77
40%	0.86	0.84	0.83	0.82	0.80
30%	1.05	0.95	0.91	0.89	0.84

[a] See text for further explanation

More realistically, all the apparently incident cases at age 30 that are actually prevalent cases should not be considered as already being diagnosed at age 18; some of them would be diagnosed also between age 18 and 27. However, that is not important for the argument. These diseases would also affect the first-birth probabilities, in a way similar to what we have assumed above. (Note that in the fertility model, the key independent variable is whether the person currently has CD, not whether the person had CD at age 18.) Furthermore, reproduction after age 18 may influence the chance of developing and being diagnosed with CD, but this effect may be about the same as the one that exists at age 30, so it would contribute to making our estimates less biased than if reality is as assumed above. Similarly, some of the D_1 persons with an earlier CD diagnosis that do *not* present with the disease at

age 30, and some of the U with an earlier UC diagnosis, may have been diagnosed at age 18-27 rather than before age 18. However, this is even less problematic, since these groups are unimportant in the argumentation.

In parts of the analysis, we are interested not only in the effect of being childless rather than a parent, but also the effect of time since last birth. To see how much effects of CD on childbearing and misclassification of prevalent cases as incident cases contribute to those effects, it would be necessary to take also second and higher-order births into account. This would require more complex calculations, possibly in the form of Monte Carlo simulations.

Web Appendix 6: Effect of education and reverse causality

The estimated association between education and IBD risks might reflect that some of the cases are actually prevalent cases, and that this earlier disease has influenced the schooling. In support of that idea, supplementary analysis showed that CD indeed reduces women's (but not men's) probability of taking further education (estimates not shown), in line with studies indicating particularly severe symptoms among women (19). However, although the effect of education may actually be weaker than suggested by our estimates, this should not cause any concern about the estimated effects of parenthood on IBD risks. Education is only a moderately important control variable (not shown), and to the extent that the educational level reflects the existence of an earlier diagnosis, controlling for it only produces more reasonable estimates of the parenthood effects.

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