**Ban L, Tata LJ, Humes DJ, et al. Decreased fertility rates in 9639 women diagnosed with inflammatory bowel disease: a United Kingdom population-based cohort study.**

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**Decreased fertility rates in 9639 women diagnosed with inflammatory bowel disease: a United Kingdom population-based cohort study.**

Short title: Fertility rate in women with IBD

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**Abbreviations:** 95%CI=95% confidence interval; CD=Crohn's disease; AFRR=adjusted fertility rate ratio; IBD=inflammatory bowel disease; IQR=interquartile range; THIN=The Health Improvement Network; UC=ulcerative colitis

**Keywords:** inflammatory bowel disease; fertility rate; surgery for IBD; epidemiology

**Summary**

**Background**

Clinical studies have reported reduced fertility in women with inflammatory bowel disease(IBD).

**Aim**

To compare fertility rates in women with IBD to those in women without IBD and assess whether the relative fertility differed following IBD diagnosis, flares, and surgery.

**Methods**

Women aged 15 to 44 years in 1990-2010 were identified from a UK primary care database. We estimated overall and age-specific fertility rates by 5-year age bands for women with and without IBD. We used Poisson regression to calculate fertility rate ratios(AFRR), adjusted for age, smoking and socioeconomic deprivation.

**Results**

There were 46.2 live births per 1,000 person-years (95% confidence interval[95%CI];44.6-47.9) in 9,639 women with IBD and 49.3 (95%CI;49.2-49.5) in 2,131,864 without (AFRR;0.93;95%CI;0.89-0.96). Excluding periods of contraception use the AFRR was 0.99 (95%CI;0.95-1.03). Before diagnosis, the AFRR for women with UC was 1.07 (95%CI;0.99-1.16) and was 0.88 (95%CI;0.81-0.97) for women with CD. After diagnosis, AFRRs were 0.87 (95%CI;0.82-0.94) for CD and 0.92 (95%CI;0.86-1.00) for UC. The fertility rate was lower following flares (AFRR;0.70;95%CI;0.59-0.82) or surgery (AFRR;0.84;95%CI;0.77-0.92). Women with pouch and non-pouch surgery had similar overall fertility though the reduction after surgery was greater for pouches (AFRR;0.48;95%CI;0.23-0.99) .

**Conclusions**

Women with Crohn's disease have marginally lower fertility rates. These rates decreased following flares and surgical interventions. Fertility rates returned almost to normal when women were not prescribed contraception but the reduction following surgical intervention remained. As the lifetime

effect of pouch versus non-pouch surgery on fertility is small, the reduction post pouch surgery should be interpreted with caution.

## INTRODUCTION

Inflammatory bowel disease (IBD) is commonly diagnosed in women of childbearing age with about 50% of women diagnosed under age 30 and 25% of women having their first pregnancy after diagnosis[1]. It is unsurprising therefore that these patients are concerned about fertility and how it may be affected by their disease and related medical and surgical treatments. Overall, previous research suggests that women with Crohn's disease (CD) but not ulcerative colitis (UC)[2] have lower live-birth fertility rates, although women with UC who have an ileoanal pouch report higher rates of involuntary infertility[3,4]. Many previous studies however are small and lack proper comparisons from the general female population without IBD. Since previous studies have generally used questionnaires to collect women's reproductive history following their IBD diagnosis[5–10], they may have been prone to recall bias. Furthermore, studies reporting reduced fertility or fecundity in women after having pouch surgery[6–11] have not considered any decrease in the light of a woman's overall fertility plan and have not directly compared fertility in women following pouch surgery to women with non-pouch surgery.

We conducted a very large cohort study of women of childbearing age to examine absolute and relative fertility as measured by the incidence rate of live births in women with IBD, using United Kingdom (UK) primary care data. Our objectives were to compare fertility in women with IBD to those in the general female population, to assess whether relative fertility was affected by IBD diagnosis, IBD flares around conception, contraceptive use, or major bowel surgery for IBD, and in women with UC to examine the fertility rates for women with pouch and non-pouch surgery separately.

## MATERIALS AND METHODS

### Study population

From The Health Improvement Network (THIN), we identified all women aged 15-44 years registered with a general practice between 1990 and 2010. THIN is an electronic database containing routinely-recorded diagnoses, medical events, and drug prescriptions from UK primary care and has been previously validated for use in pharmacoepidemiology research[12]. Women with IBD were defined as those with a medical Read code for a diagnosis of IBD in their primary care records. Each woman with IBD was assigned an IBD diagnosis date corresponding to the date of her first recorded IBD diagnosis or the date of her first prescription of 5-aminosalicylic acid, whichever was earlier. Women with IBD were classified as having CD if they had diagnoses specifying this condition regardless of whether they also had diagnoses of UC, whereas women were classified as having UC if they had a recording of UC only. The small proportion of women for whom neither UC or CD were coded, but only non-specific IBD codes are included within the overall IBD cohort only. For women with IBD we identified records of all major bowel surgery (intestinal resection with and without an ileoanal pouch formed) in their medical records. All women with no evidence of IBD in their medical records formed our comparison cohort, which are a good representation of the general population of women of childbearing age[13]. We identified all live births for women in the IBD and comparison cohorts over the study period.

### Statistical analysis

Using Stata SE 11.0 (Stata Corp., College Station, TX, USA) we calculated the overall fertility rate as the number of live births per 1,000 person-years of follow-up when women were between age 15 and 44 years and age-specific fertility rates in 5-year age bands. We used Poisson regression adjusting for maternal smoking (classified as ever-smoker in women ever recorded as having smoked or never-smoker where no such record was present) and socioeconomic status (defined using quintiles of the Townsend Deprivation Index) to calculate both age-specific fertility rate ratios (AFRRs) comparing women with and without IBD and also an overall (AFRR) considering women in all age bands and adjusting additionally for age in 5-year bands. We repeated the same analyses for IBD subtypes (CD

and UC) separately. Eight hundred and ten women with codes for IBD but not CD or UC (8% of the overall IBD cohort) were excluded from the disease subtype analyses.

**Before and after IBD diagnosis**

To investigate whether women's fertility relative to the general population varied in relation to their diagnosis of IBD, we estimated the overall and age-specific fertility rates after splitting the follow-up time of women with IBD into before and after the IBD diagnosis date. We estimated the AFRRs of women with IBD before or after diagnosis relative to the general population comparison cohort.

**IBD flares around conception**

To assess the effect of disease activity, for women with IBD we used corticosteroid prescriptions as a surrogate measure for flares. A flare was defined as the period following a new corticosteroid prescription after at least four months without such a prescription, as previously validated within this database[14]. We considered each flare to last for at least three months and remission periods were defined as time when women with IBD were not having a flare. We estimated the proportions of women with flares in each age band and the average length of flares. We calculated fertility rates in women with IBD separately for time periods during which conception would have occurred during an IBD flare (i.e. births happening 9 months after a flare), and time periods when it would have occurred in remission, and compared the rates to the comparison cohort. We did this for IBD overall and for CD and UC separately. Analyses were repeated assuming flare lengths of 1.5 and 6 months also to examine the sensitivity of the analysis to these assumptions.

**Fertility rates in time periods not affected by contraceptive use**

To explore the potential effect of voluntary childlessness for women with IBD, we conducted an additional analysis to examine the fertility rates after excluding time periods in which women were prescribed contraception. We assessed prescriptions of combined oral contraceptive pills, progestogen-only pills, progestogen-only implants and injections, copper intrauterine devices, and the levonorgestrel-releasing intrauterine system. We defined women as having continuous contraceptive use if the subsequent prescription happened within 28 days of the end of the previous one. For women with progestogen-only implants, copper intrauterine devices and the levonorgestrel-releasing

intrauterine system, we assumed the effects of these contraceptive methods lasted for the periods for which they were prescribed (3 years for progestogen-only implants, 10 years for copper intrauterine devices, and 5 years for the levonorgestrel-releasing intrauterine system) unless their medical records indicated they stopped these methods at earlier dates. For women with and without IBD we estimated fertility rates excluding the time periods during which women were covered by these contraceptives plus nine months after discontinuation, thus allowing for the average period of gestation. We calculated the AFRRs for IBD overall and for CD and UC separately, as well as for women with IBD following surgery.

**Major bowel surgery and pouch surgery**

Among women with IBD, we estimated fertility rates in those who had records of intestinal resections separately from those without intestinal resections, and compared the rates to those in the general population comparison cohort to ensure they were comparable with our primary analyses. To assess whether women's fertility rates varied only in the time following surgery, we then separated the follow-up time before and after a woman's surgical period (defined as before the first ever surgical operation up to nine months after her last operation, thus allowing for women's recovery from surgical intervention) and investigated the fertility in these periods relative to the comparison cohort. We repeated the same analyses for CD and UC separately. In women with UC, we conducted a sensitivity analysis to separately estimate the fertility rates in women who had an ileoanal pouch and those having a colectomy but who did not go on to have a pouch formed and to assess the rates both before and after surgery relative to the comparison cohort.

**Perianal disease**

We defined the presence of perianal disease as ever having a diagnosis for fistula, abscess or fissure and or a surgery for the disease in a woman's medical records. We carried out an analysis of the overall AFRR in women with CD with or without perianal disease to assess whether by potentially decreasing desire to be sexually active or causing dyspareunia, it reduced fertility.

## RESULTS

### Study population

We identified 9,639 women with IBD (4,475 with CD and 4,354 with UC) and 2,131,864 women without IBD (Table 1). The median age at start of follow-up was 30.1 years (interquartile range [IQR] 23.5-36.8) for women with IBD and 26.8 (IQR 20.5-34.1) for women without IBD, and their median follow-up time was 5.7 years (IQR 2.5-10.5) and 3.5 years (1.4-7.4) respectively. In women aged 20-24 years, 67.3% of women with IBD were using a contraceptive which was 11.0% higher than women without IBD and the increased use of contraceptives in women with IBD compared to women without IBD were also found in all other age groups (Table 1).

Median age at IBD diagnosis was 29.3 years (IQR 22.8-37.7) being 26.9 years (IQR 21.4-35.0) for CD and 31.6 years (IQR 24.5-39.1) for UC. Women with UC were less likely to be from socioeconomically deprived areas and to be smokers compared with women with CD (Table 1). Of women with IBD 21.9% aged 15-19 years had a flare and 32.0% of those aged 40-44 years. The average length of flares was 3.0 months (IQR 3.0-5.2) which was similar between women with CD and UC (Table 1).

### Overall and age-specific fertility rates and rate ratios

We identified 3,057 live births in women with IBD (1,399 for CD and 1,390 for UC). The overall fertility rate was 49.3 live births per 1,000 person-years (95% confidence interval [95%CI] 49.2-49.5) in the general population, and was slightly lower in women with IBD (46.2, 95%CI 44.6-47.9; AFRR 0.93, 95%CI 0.89-0.96). However, this reflected lower rates in women with CD (45.3, 95%CI 42.9-47.7; AFRR 0.88, 95%CI 0.83-0.92 compared with the general population) but not in women with UC (47.6, 95%CI 45.2-50.2; AFRR 0.99, 95%CI 0.94-1.04) (Table 2). Age-specific fertility rates, however, showed that the relative difference in fertility rates between women with and without IBD varied by age (Table 2 and Figure 1a). Compared with women without IBD, women with CD had similar fertility rates in the 20-24, 25-29 and 40-44 year age bands but had slightly lower fertility rates in other age bands (Table 2).

### Fertility before and after diagnosis of IBD

When dividing the follow-up time in women with IBD into before or after IBD diagnosis, their overall fertility rate was 50.6 live births per 1,000 person-years (95%CI 47.9-53.4) before IBD diagnosis and 43.4 (95%CI 41.4-45.5) after diagnosis (Figure 1b). Compared with women without IBD, the overall AFRR was 0.98 (95%CI 0.93-1.04) before IBD diagnosis but 0.89 (95%CI 0.85-0.94) after (Table 3). When looking at the influence of age upon this relationship, fertility in women with IBD was slightly higher before diagnosis than after especially before age 30 years but similar after that (Figure 1b). Subdividing by IBD type, compared with women without IBD, the fertility rate was statistically significant lower in women with CD both before and after diagnosis (AFRR 0.88 and 0.87, 95%CI 0.81-0.97 and 0.82-0.94 for before and after CD diagnosis respectively). For UC however, the AFRR was slightly higher before diagnosis (AFRR 1.07, 95%CI 0.99-1.16), but lower after diagnosis (AFRR 0.92, 95%CI 0.86-1.00).

**IBD flares around conception**

In women with IBD, the overall fertility rates were 35.6 live births per 1,000 person-years (95%CI 30.7-41.2) in the 9 month periods following flares and 47.1 (95%CI 45.4-48.8) following periods without flares. The overall AFRR compared with women without IBD was 0.70 (95%CI 0.59-0.82) and 0.95 (95%CI 0.91-0.98) respectively (Supplementary Table 1). After additionally adjusting for contraceptive use for women with flares, the results remained almost unchanged (Supplementary Table 1).The age-specific AFRRs were also lower in the periods following flares than following periods without flares. Similar patterns were found when examining women with CD and UC separately (Supplementary Table 1). These figures were not appreciably changed by varying the length of flares between 1.5 and 6 months.

**Fertility rates in time periods not affected by contraceptive use**

After excluding time periods during which women used contraceptives, we found similar overall fertility rates in women with and without IBD (fertility rates=62.8 and 63.4 live births per 1,000 person-years, 95%CIs 63.2-63.5 and 60.5-65.2, AFRR=0.99, 95%CI 0.95-1.03) and in women with CD and UC separately (62.9 and 63.6 live births per 1,000 person-years, 95%CIs 59.5-66.5 and 60.2-67.3, AFRRs compared to women without IBD=0.95 and 1.05, 95%CIs 0.89-1.01 and 0.99-1.12 respectively). Compared with women without IBD, the age-specific fertility rates in women with IBD

were slightly lower in the youngest and oldest age groups but not in middle age groups (Supplementary Table 2).

**Fertility in women with bowel surgery**

In women with IBD, 1,618 had intestinal resection (1,153 for CD and 452 for UC). Women's median age at the 1st surgical intervention was 28.9 years (IQR 22.9-37.1) (Table 1). In those women with UC who had pouch surgery, the median age at which this was performed was 32.7 years (IQR 25.6-39.2). The fertility rate was 41.8 live births per 1,000 person-years (95%CI 37.3-45.6) in the IBD cohort with intestinal resection but 47.2 (95%CI 45.4-49.1) in the IBD cohort without surgery (Figure 2a). Compared with women without IBD, the overall AFRR was 5% lower in women with IBD who did not have surgery (AFRR 0.95, 95%CI 0.91-0.99) and was 16% lower in women with surgery (AFRR 0.84, 95%CI 0.77-0.92) (Table 4). In addition, the fertility rate was lower after surgery (AFRR 0.81, 95%CI 0.71-0.94) but not before surgery (AFRR 0.97, 95%CI 0.86-1.10) (Supplementary Table 3) when compared to those women without IBD. Fertility rates varied substantially by age (Figure 2). Compared with women without surgery for IBD, women with surgery had higher fertility rates at younger ages (age 15-19 and 20-24 years) but lower fertility rates at older ages (Figure 2a). When examining fertility rates before and after surgery, the fertility rates were higher in women before surgery especially in women before age 30 (Figure 2b).

**Fertility in women with an ileoanal pouch surgery**

For women with UC, the overall fertility rate was 36.7 live births per 1,000 person-years (95%CI 30.5-44.2) in those who ever had a colectomy and 48.9 (95%CI 46.3-51.6) in those who did not. Compared with women without IBD, women with a record of surgery for UC had a 21% decreased overall fertility rate (AFRR 0.79, 95%CI 0.65-0.96) (Table 4) and this reflected a lower fertility rate after surgery (AFRR 0.70; 95%CI 0.50-0.99) (Supplementary Table 3). Though the overall fertility rate was lower, it was similar in women with both pouch (AFRR 0.75; 95%CI 0.55-1.01) and non-pouch surgery (AFRR 0.82; 95%CI 0.63-1.05). The fertility rates were 23.4 live births per 1,000 person-years (95%CI 12.2-45.0; AFRR 0.48, 95%CI 0.23-0.99 compared with women without IBD) after pouch surgery and 32.59 (95%CI 22.35-47.52; AFRR=0.83, 95%CI 0.57-1.22) after non-pouch surgery (Supplementary Table 3). Compared with women without IBD, women having an ileoanal pouch had similar fertility rates (54.7 live births per 1,000 person-years, 95%CI 38.3-78.3; AFRR 1.08, 95%CI 0.76-1.52) before

the operation of colectomy (Supplementary Table 3). Though the difference between the groups was not significant, women with non pouch surgery had slightly lower fertility before their operations were completed (AFRR 0.86, 95%CI 0.61-1.21) than did those with pouches (AFRR 1.08, 95%CI 0.76-1.52), and had higher fertility afterwards (AFRR 0.83, 95%CI 0.57-1.22) compared to those with pouches (AFRR 0.48, 95%CI0.23-0.99). The reduced fertility rates following bowel surgery (either pouch or non-pouch surgery) remained almost unchanged after excluding the time periods affected by contraceptive use (Supplementary Table 3).

**Perianal disease**

There were 16.5% of women with CD ever with perianal disease. When examining the role of perianal disease, we found that the AFRR was 0.90 (95%CI 0.79-1.02) for women with CD and perianal disease and 0.87 (95%CI 0.82-0.93) for women with CD but without perianal disease.

## DISCUSSION

### Principal findings

We have shown that over their reproductive years women with CD have slightly lower fertility rates than women without IBD. Women with UC however have an overall fertility rate similar to that of the general female population. There is also a decreased fertility rate after CD or UC diagnosis and this mainly affects women before age 30. There is a further decrease in fertility rates in periods following flares and after surgical intervention, especially following pouch surgery. Overall fertility in women with pouch surgery however is similar to women with non-pouch surgery. Some of the apparent adverse effects of pouch surgery among women with UC may therefore be due to family planning as women who have pouch surgery have a higher fertility rate before surgery, suggesting women electively complete their families before pouch surgery. Further evidence of the role of family planning and voluntary childlessness is provided by a comparison of fertility rates during periods when contraception was not prescribed. During these periods we found no significant reduction in overall fertility rate in women with either CD or UC; however, the fertility rate remained lower for women after surgery. The average diagnosis of CD is close to the average age of first birth for women in the UK (the average age of first birth for women was 27.0 years in 1999[15]), and is about five years earlier than the average age of UC diagnosis, so it is possible that CD diagnosis more commonly interrupts women's fertility plans.

Our findings provide population-level estimates that enable women with IBD to have realistic comparisons of their likelihood of childbearing overall and following surgery in comparison with women in the general population, and will thus facilitate evidence-based (family planning) decisions between health care professionals and women with IBD.

### Strengths and limitations

Because our study is based upon analysis of a large population-based cohort of women of childbearing age, it permits us to compare fertility rates in unbiased samples of women with IBD and without. This should allow our results to be generalisable to the UK population. The size of the database and the consequent study also allows us the power to provide reasonably precise estimates

for our comparisons, and to subdivide time and patient groups to separately study women of differing ages, with UC and CD, both with and without flares, surgery or use of contraceptives, and before and after surgery. A great strength of our study is that we were able to examine contraceptive use to minimise the potential confounding effect of voluntary childlessness. Although the small minority of contraception provided from family planning clinics in the UK is not coded in THIN, we believe it unlikely this would differ substantially between women with and without IBD. A slightly greater problem occurs with the recording of immunosuppression which is of obvious importance in IBD. Since much of this is prescribed in hospitals in the UK, and we have only GP prescription data, we are unable to assess any effect which it may have.

An inevitable weakness of any large study using routinely collected data is that researchers cannot validate the diagnoses of individuals involved. This might appear to be a particular problem in the current study since in the UK IBD is diagnosed in secondary care, and we are using primary care data. Secondary care information, especially major medical events and medical diagnoses are however routinely recorded in UK primary care records following discharge communication, and the recording of IBD diagnoses in primary care has been shown to be highly accurate and complete[16].

Similar concerns might be raised over the recording of births since the overall fertility rate in our population at 49.3 live births per 1,000 persons-years is slightly lower than the average national general fertility rate over the same period as our study. Compared with the national average the fertility rates in the comparison group are consistently lower in all 5-year age groups. However the variation in fertility in different maternal age groups is similar to the national trend. We believe this could be due to the fact that general practices that contribute information to the THIN database are in less socioeconomically deprived areas, since previous research has shown that more people in THIN live in socioeconomically more affluent areas[17] than the general UK population. Nevertheless, we cannot think of any reason why this would lead to any systematic differences in recording of live births between women with IBD and without IBD affecting the internal validity of our findings, particularly as we have included socioeconomic deprivation in our study and the differences between women with and without IBD are marginal. In addition, although we have an average of 3.5 years (IQR 1.4-7.4) follow-up data over the study period, longer for women with IBD than women without IBD, we do not have women's complete reproductive history and therefore are unable to estimate the total attained

family size for the vast majority of the women. However, unlike most previous studies that expressed fertility as number of children per woman or the number of pregnant women in the population, we defined fertility as the number of live births per 1,000 person-years and calculated the incidence of live births with consideration of the different length of follow-up for women with and without IBD. If women included in a study have not reached the end of their reproductive lifespan, not accounting for age-specific follow-up time could distort comparisons because of altered family planning.

Finally the identification of flares of IBD relies on prescriptions of corticosteroid. Though this has been validated (to show that flares identified really are likely to be flares), it may miss flares treated exclusively with drugs containing 5-aminosalicylic acid.

**Interpretation in the context of previous studies**

Our study calculates fertility rates as numbers of live births per 1,000 person-years of follow-up for women between ages 15 and 44 years, and not fertility (the capacity to produce offspring), or fecundability (the probability of becoming pregnant per month of unprotected intercourse).Using slightly different measurements of fertility, previous studies found that compared with women without the disease, women with CD have lower fertility[18–20] but not women with UC[10,19,21], which is consistent with our study. For example, Moody *et al.* who interviewed over 600 women with IBD in Leicester, UK about their reproductive histories and compared them to Census data found that women with CD had on average fewer live births per woman (1.2 live births per woman) than the general population but women with UC were more similar to the general population (1.9 live births per woman)[19]. In line with our finding that fertility was lower after diagnosis than before, the authors found more live births before diagnosis than after diagnosis for women with both CD and UC. This study however did not examine the effect of surgical intervention, nor did it present the average follow-up period for women with IBD. Olsen and colleagues who did examine fecundity (defined as the probability of becoming pregnant per month with unprotected intercourse) before and after surgical intervention by restorative proctocolectomy in women with UC from Sweden and Denmark[10] found that compared with women in the general population, the fecundability was higher before diagnosis (fecundability ratio 1.46, 95%CI 1.16-1.85) but much lower after pouch surgery (fecundability ratio 0.20, 95%CI 0.15-0.28). Our own findings though less extreme are similar.

Although a number of previous studies have suggested that women who undergo pouch surgery have decreased fecundability (perhaps due to adhesion formation in the pelvis)[22], more recent evidence suggests that a higher proportion of women become pregnant spontaneously if they have laparoscopic rather than open pouch surgery[23]. Since the laparoscopic approach is uncommon in our study population, we were unable to differentiate the effect from open pouch surgery and therefore cannot inform debate on whether laparoscopic surgical intervention reduces issues of post surgical hypo-fertility by reducing adhesions in the pelvis. The mechanism of post pouch reduction in fertility however remains unclear. A US study[24] found that pouch function and pregnancy-related complications in pregnant women with a pouch (largely with open pouch surgery) were generally similar to what could be expected in the general female population, suggesting that at least some of the previous concerns about the physical interaction of the pregnant uterus and pouch may have been overstated. It is therefore interesting to consider other potential mechanisms for the common finding of lower fertility rates in this patient group. As early as the 1970s the possibility that interactions between IBD and fertility might be due to frequency of intercourse rather than function of the reproductive organs was considered[25]. More recently there has been clear evidence that at least some of the sub-fertility in IBD may be voluntary[5,20,26,27]. Our findings that women with IBD (both CD and UC) were more likely to use contraceptives than women without IBD and had similar overall fertility rates after excluding time periods with contraceptive use are in line with this potential explanation. Moreover, our finding that the overall fertility is similar in women with pouch and non-pouch surgery and that fertility is supra-normal in women before pouch surgery may in this context therefore suggest that women undergoing a pouch operation sometimes electively complete their family prior to surgery with an inevitable compensatory reduction in fertility thereafter. However, that the fertility rates following pouch and non-pouch surgery remained reduced after excluding time period affected by contraceptive use may suggest that surgical intervention has some biological effect on women's fertility.

**Conclusion**

Our study found only slightly decreased fertility rates in women with CD and in women who had surgical intervention compared to the general female population, which is reassuring for women with IBD and their health care providers and thus provides vital information for women's family planning.

We also found that these reductions in fertility were non-significant if only time when no contraception was prescribed were considered. Moreover, since the overall fertility rate is similar in women with pouch and non-pouch surgery, any potential harmful effects of pouch surgery should be interpreted cautiously. Women should be advised about their potential fertility according to their existing reproductive history, presence of acute flares and need for surgical intervention.

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Table 1 Characteristics of study population (N=2,141,503)

| | **Comparison cohort (n=2,131,864)** | | **IBD cohort[a] (n=9,639)** | | **CD cohort (n=4,475)** | | **UC cohort (n=4,354)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **p** |
| **Age at start of follow-up,** years (Median, IQR) | 26.8 | *20.5-34.1* | 30.1 | *23.5-36.8* | 28.7 | *22.5-35.7* | 31.5 | *25.1-37.5* | <0.001 |
| **Townsend deprivation index** | | | | | | | | | |
| 1 (Least deprived) | 439,474 | *20.6* | 2,323 | *24.1* | 998 | *22.3* | 1,132 | *26.0* | |
| 2 | 385,636 | *18.1* | 2,071 | *21.5* | 964 | *21.5* | 944 | *21.7* | |
| 3 | 409,860 | *19.2* | 1,881 | *19.5* | 892 | *19.9* | 845 | *19.4* | |
| 4 | 398,434 | *18.7* | 1,635 | *17.0* | 763 | *17.1* | 712 | *16.4* | |
| 5 (Most deprived) | 303,222 | *14.2* | 1,088 | *11.3* | 564 | *12.6* | 430 | *9.9* | |
| Missing | 195,238 | *9.2* | 641 | *6.7* | 294 | *6.6* | 291 | *6.7* | <0.001 |
| **Smoker ever** | 878,697 | *41.2* | 4,953 | *51.4* | 2,492 | *55.7* | 2,008 | *46.1* | <0.001 |
| **Contraceptive use**, in women aged | | | | | | | | | |
| 15-19 years | 229,382 | *46.3* | 826 | *60.1* | 476 | *60.6* | 259 | *55.5* | <0.001 |
| 20-24 years | 388,790 | *56.3* | 1,768 | *67.3* | 941 | *67.0* | 651 | *66.2* | <0.001 |
| 25-29 years | 403,636 | *53.6* | 2,338 | *62.9* | 1,174 | *62.1* | 961 | *63.8* | <0.001 |
| 30-34 years | 331,889 | *46.2* | 2,358 | *54.7* | 1,136 | *56.7* | 1,021 | *52.5* | <0.001 |
| 35-39 years | 235,309 | *35.2* | 1,838 | *40.8* | 815 | *41.5* | 874 | *40.8* | <0.001 |
| 40-44 years | 141,758 | *22.7* | 1,231 | *27.0* | 512 | *27.2* | 611 | *26.9* | <0.001 |
| **Average age at childbirth,** years (Median, IQR) | 29.7 | *25.3-33.6* | 30.5 | *26.8-34.1* | 29.9 | *25.9-33.5* | 31.1 | *27.6-34.7* | <0.001 |
| **Age at IBD diagnosis,** years (Median, IQR) | --- | | 29.3 | *22.8-37.7* | 26.9 | *21.4-35.0* | 31.6 | *24.5-39.1* | <0.001 |
| **Age at 1st bowel surgery[b],** years (Median, IQR) | --- | | 28.9 | *22.9-37.1* | 28.0 | *22.5-35.7* | 31.6 | *24.0-40.3* | <0.001 |
| **Age at pouch surgery[c],** years (Median, IQR) | --- | | --- | | --- | | 32.7 | *25.6-39.2* | |
| **IBD flares,** in women aged | | | | | | | | | |
| 15-19 years | --- | | 301 | *21.9* | 192 | *24.4* | 104 | *22.3* | <0.001 |
| 20-24 years | --- | | 741 | *28.2* | 447 | *31.8* | 260 | *26.4* | <0.001 |
| 25-29 years | --- | | 1,165 | *31.3* | 661 | *35.0* | 465 | *30.9* | <0.001 |
| 30-34 years | --- | | 1,349 | *31.3* | 658 | *32.8* | 630 | *32.4* | <0.001 |
| 35-39 years | --- | | 1,398 | *31.1* | 629 | *32.0* | 706 | *32.9* | <0.001 |

| | Comparison cohort (n=2,131,864) | | IBD cohort[a] (n=9,639) | | CD cohort (n=4,475) | | UC cohort (n=4,354) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **p** |
| 40-44 years | --- | | 1,456 | *32.0* | 628 | *33.4* | 771 | *34.0* | <0.001 |
| **Average length of IBD flares,** months (Median, IQR) | --- | | 3.0 | *3.0-4.9* | 3.0 | *3.0-5.2* | 3.0 | *3.0-4.8* | <0.001 |

[a] 810 women with IBD but CD or UC not specified, the characteristics of which were similar to the overall IBD group;

[b] Based on 1,618 women with bowel surgery (1,153 for CD and 452 for UC);

[c] Based on 147 women with pouch surgery;

IBD=inflammatory bowel disease; CD=Crohn's disease; UC=ulcerative colitis; IQR=interquartile range

Table 2 Overall and age-specific fertility rate ratios for inflammatory bowel disease

| **Age in years** | **Comparison cohort (n=2,131,864)** | | **IBD cohort (n=9,639)** | | | **CD cohort (n=4,475)** | **UC cohort (n=4,354)** |
|---|---|---|---|---|---|---|---|
| | **No. live births** | **Person-years** | **No. live births** | **Person-years** | **AFRR (*95% CI*)** | **AFRR (*95% CI*)** | **AFRR (*95% CI*)** |
| 15-19 | 30,896 | 1,323,753 | 78 | 4,406 | 0.71 (*0.56-0.89*) | 0.73 (*0.55-0.96*) | 0.73 (*0.48-1.09*) |
| 20-24 | 91,405 | 1,537,861 | 412 | 7,171 | 0.94 (*0.85-1.03*) | 0.89 (*0.78-1.02*) | 0.95 (*0.80-1.12*) |
| 25-29 | 148,831 | 1,795,279 | 922 | 10,623 | 1.02 (*0.95-1.08*) | 0.96 (*0.88-1.06*) | 1.10 (*1.00-1.22*) |
| 30-34 | 157,950 | 1,953,239 | 1,035 | 13,571 | 0.92 (*0.87-0.98*) | 0.87 (*0.80-0.96*) | 0.97 (*0.89-1.06*) |
| 35-39 | 79,349 | 2,030,425 | 520 | 15,092 | 0.87 (*0.80-0.96*) | 0.79 (*0.69-0.91*) | 0.96 (*0.85-1.08*) |
| 40-44 | 15,009 | 1,972,991 | 90 | 15,265 | 0.78 (*0.62-0.98*) | 0.83 (*0.61-1.14*) | 0.76 (*0.56-1.02*) |
| **Overall (All ages)** | **523,440** | **10,613,550** | **3,057** | **66,128** | **0.93 (*0.89-0.96*)** | **0.88 (*0.83-0.92*)** | **0.99 (*0.94-1.04*)** |

AFRR=fertility rate ratio comparing women with IBD (or CD or UC separately) to women in the comparison cohort without IBD, adjusted for maternal smoking and socioeconomic status (with additional adjustment for maternal age for overall fertility rate ratios);

95%CI=95% confidence interval; IBD=inflammatory bowel disease; CD=Crohn's disease; UC=ulcerative colitis

Table 3 Age-specific fertility rate ratios before and after diagnoses of inflammatory bowel disease (IBD) (N=5,803 and 8,685 respectively) compared with women without IBD (N=2,131,864)

| Age in years | Before IBD diagnosis | | After IBD diagnosis | |
|---|---|---|---|---|
| | **AFRR** | ***95% CI*** | **AFRR** | ***95% CI*** |
| **IBD cohort** | | | | |
| 15-19 | 0.71 | *0.54-0.93* | 0.69 | *0.45-1.06* |
| 20-24 | 1.03 | *0.91-1.17* | 0.84 | *0.72-0.97* |
| 25-29 | 1.12 | *1.02-1.22* | 0.94 | *0.86-1.03* |
| 30-34 | 0.93 | *0.84-1.02* | 0.92 | *0.85-0.99* |
| 35-39 | 0.89 | *0.76-1.04* | 0.87 | *0.78-0.97* |
| 40-44 | 0.84 | *0.58-1.23* | 0.75 | *0.56-1.00* |
| **Overall** (All ages) | 0.98 | *0.93-1.04* | 0.89 | *0.85-0.94* |
| **CD cohort** | | | | |
| 15-19 | 0.72 | *0.52-0.98* | 0.76 | *0.45-1.26* |
| 20-24 | 0.93 | *0.77-1.12* | 0.86 | *0.72-1.03* |
| 25-29 | 1.02 | *0.88-1.17* | 0.93 | *0.82-1.05* |
| 30-34 | 0.80 | *0.67-0.96* | 0.90 | *0.81-1.01* |
| 35-39 | 0.75 | *0.56-1.00* | 0.80 | *0.68-0.94* |
| 40-44 | 0.64 | *0.32-1.28* | 0.90 | *0.59-1.37* |
| **Overall** (All ages) | 0.88 | *0.81-0.97* | 0.87 | *0.82-0.94* |
| **UC cohort** | | | | |
| 15-19 | 0.76 | *0.44-1.31* | 0.64 | *0.28-1.48* |
| 20-24 | 1.11 | *0.92-1.35* | 0.71 | *0.52-0.96* |
| 25-29 | 1.24 | *1.09-1.41* | 0.98 | *0.85-1.13* |
| 30-34 | 1.01 | *0.89-1.15* | 0.94 | *0.84-1.06* |
| 35-39 | 0.98 | *0.80-1.20* | 0.94 | *0.81-1.10* |
| 40-44 | 0.92 | *0.56-1.52* | 0.68 | *0.46-1.02* |
| **Overall** (All ages) | 1.07 | *0.99-1.16* | 0.92 | *0.86-1.00* |

AFRR=fertility rate ratio comparing women before and after IBD diagnosis to women in the comparison cohort without IBD, adjusted for maternal smoking and socioeconomic status (with additional adjustment for maternal age for overall fertility rate ratios);

IBD=inflammatory bowel disease; CD=Crohn's disease; UC=ulcerative colitis; 95%CI=95% confidence interval

Table 4 Age-specific fertility rate ratios for inflammatory bowel disease (IBD) with and without intestinal resection (N=1,618 and 8,021 respectively) compared with women without IBD (N=2,131,864)

| **Age in years** | **Without surgery** | | **With surgery** | |
|---|---|---|---|---|
| | **AFRR** | ***95% CI*** | **AFRR** | ***95% CI*** |
| **IBD cohort** | | | | |
| 15-19 | 0.70 | *0.54-0.91* | 0.71 | *0.42-1.21* |
| 20-24 | 0.90 | *0.80-1.00* | 1.12 | *0.91-1.38* |
| 25-29 | 1.03 | *0.96-1.11* | 0.94 | *0.80-1.09* |
| 30-34 | 0.96 | *0.89-1.02* | 0.77 | *0.66-0.90* |
| 35-39 | 0.91 | *0.83-1.00* | 0.70 | *0.55-0.88* |
| 40-44 | 0.79 | *0.62-1.01* | 0.73 | *0.40-1.33* |
| **Overall** (All ages) | 0.95 | *0.91-0.99* | 0.84 | *0.77-0.92* |
| **CD cohort** | | | | |
| 15-19 | 0.68 | *0.50-0.93* | 0.89 | *0.53-1.50* |
| 20-24 | 0.82 | *0.69-0.96* | 1.13 | *0.90-1.42* |
| 25-29 | 0.98 | *0.88-1.09* | 0.91 | *0.76-1.09* |
| 30-34 | 0.90 | *0.81-1.01* | 0.81 | *0.68-0.96* |
| 35-39 | 0.84 | *0.71-0.99* | 0.67 | *0.51-0.89* |
| 40-44 | 0.82 | *0.53-1.27* | 0.85 | *0.45-1.64* |
| **Overall** (All ages) | 0.89 | *0.83-0.95* | 0.85 | *0.77-0.94* |
| **UC cohort** | | | | |
| 15-19 | 0.82 | *0.52-1.31* | - | - |
| 20-24 | 0.94 | *0.79-1.12* | 1.05 | *0.63-1.73* |
| 25-29 | 1.11 | *1.01-1.23* | 1.00 | *0.74-1.36* |
| 30-34 | 1.00 | *0.92-1.10* | 0.69 | *0.51-0.95* |
| 35-39 | 0.98 | *0.86-1.11* | 0.79 | *0.52-1.22* |
| 40-44 | 0.83 | *0.60-1.14* | 0.16 | *0.02-1.13* |
| **Overall** (All ages) | 1.01 | *0.96-1.07* | 0.79 | *0.65-0.96* |

AFRR=fertility rate ratio comparing women with IBD with and without bowel surgery to women in the comparison cohort without IBD, adjusted for maternal smoking and socioeconomic status (with additional adjustment for maternal age for overall fertility rate ratios); gap in the cell indicates no outcomes.

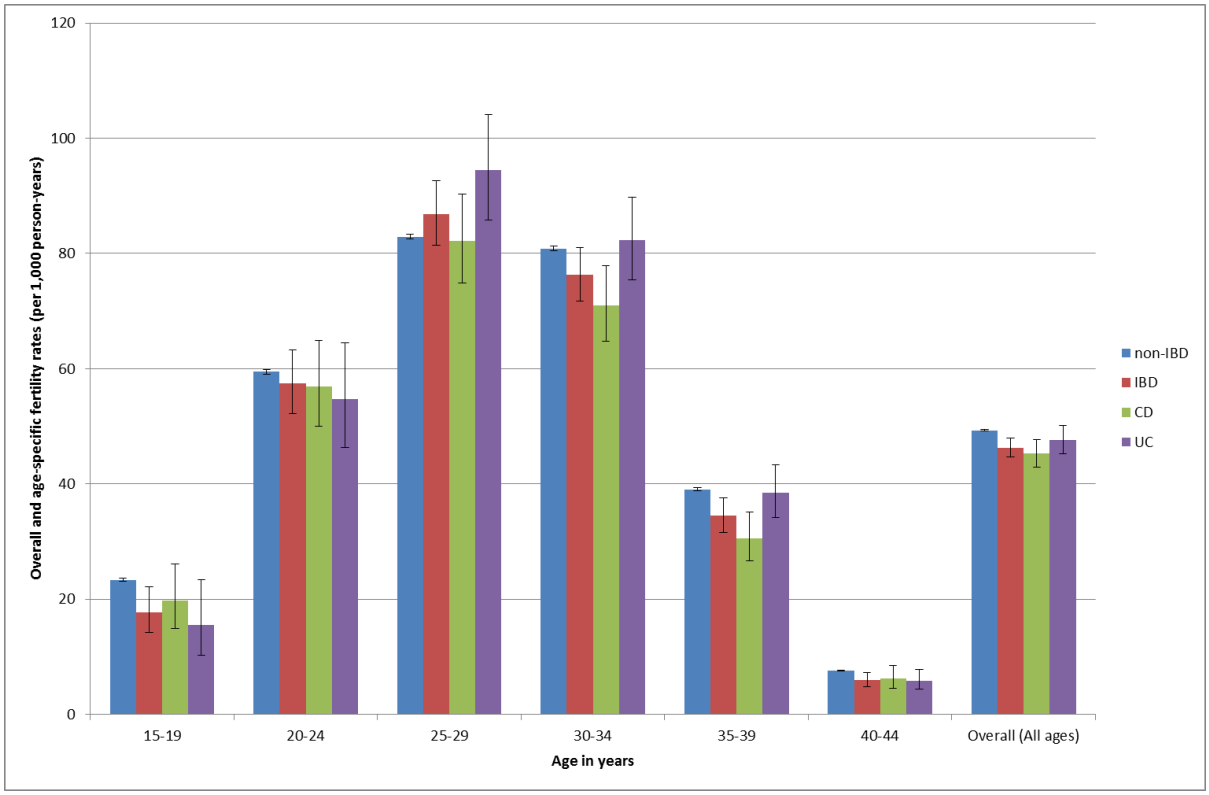
IBD=inflammatory bowel disease; CD=Crohn's disease; UC=ulcerative colitis; 95%CI=95% confidence interval

**Figure legends**

Figure 1. Age-specific fertility rates (per 1,000 person-years) for women with IBD (N=9,639) compared to women without IBD (N=2,131,864). The relative difference in fertility rates between women with and without IBD varied by age (A). The overall fertility rate was higher before IBD diagnosis than after but the difference varied by age (B).

Figure 2. Age-specific fertility rates (per 1,000 person-years) for women with IBD with bowel surgery (N=1,618) compared to women without IBD (N=2,131,864). Fertility rates in women with bowel surgery for IBD varied substantially by age and were higher at younger ages but lower at older ages (A). Fertility rates were higher in women before surgery especially in women before age 30 (B).

A




B

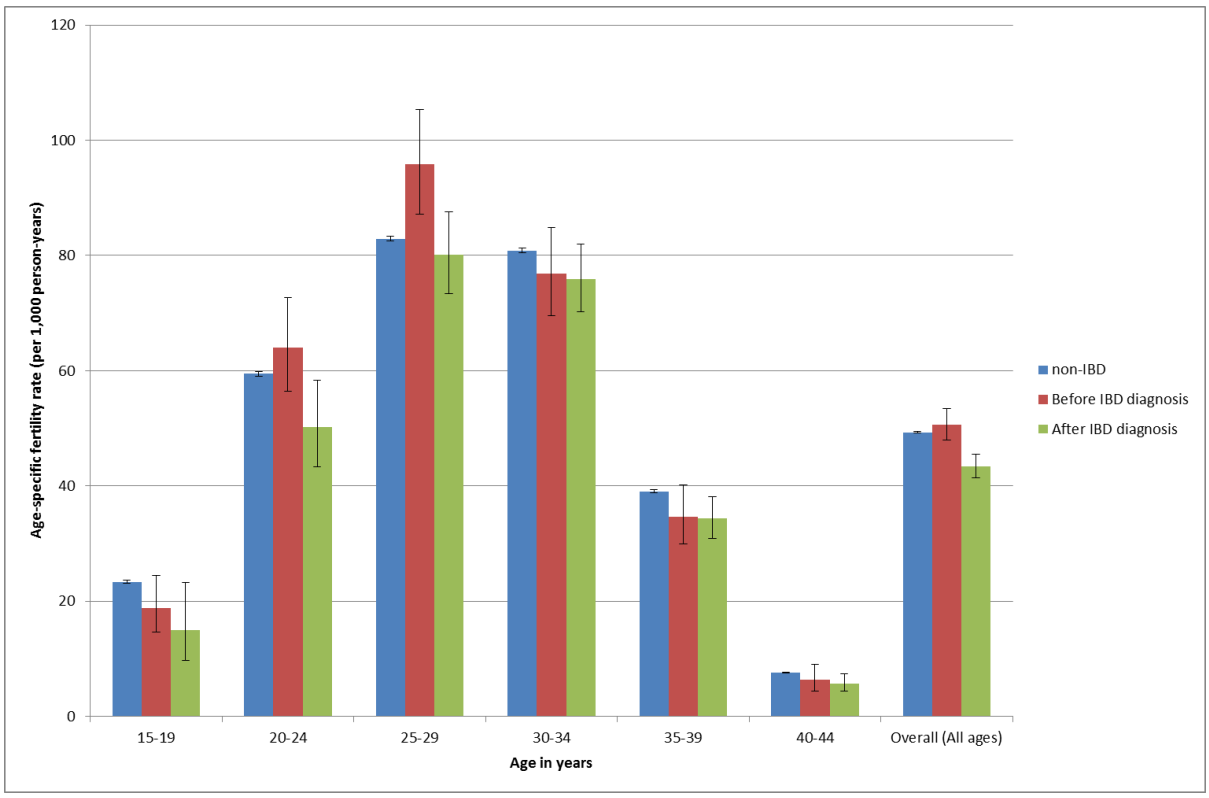
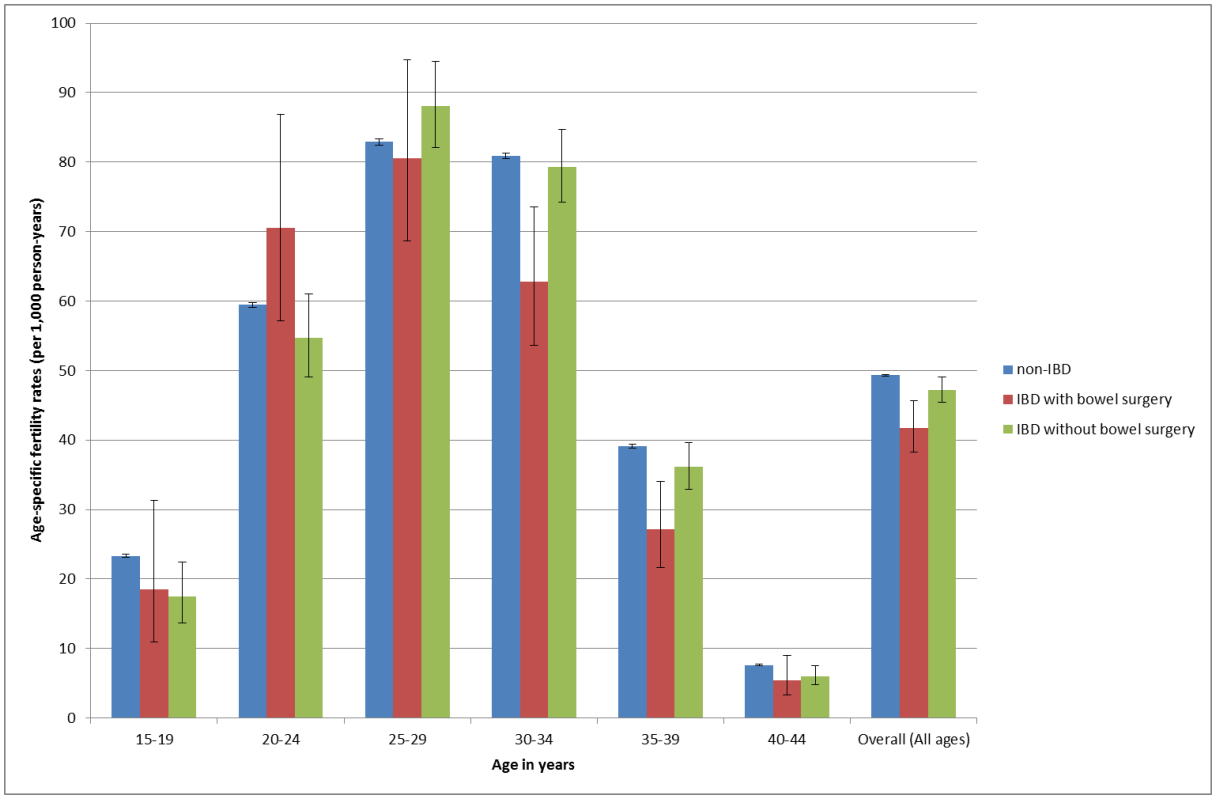



Figure 1. Age-specific fertility rates (per 1,000 person-years) for women with IBD (N=9,639) compared to women without IBD (N=2,131,864)

A




B

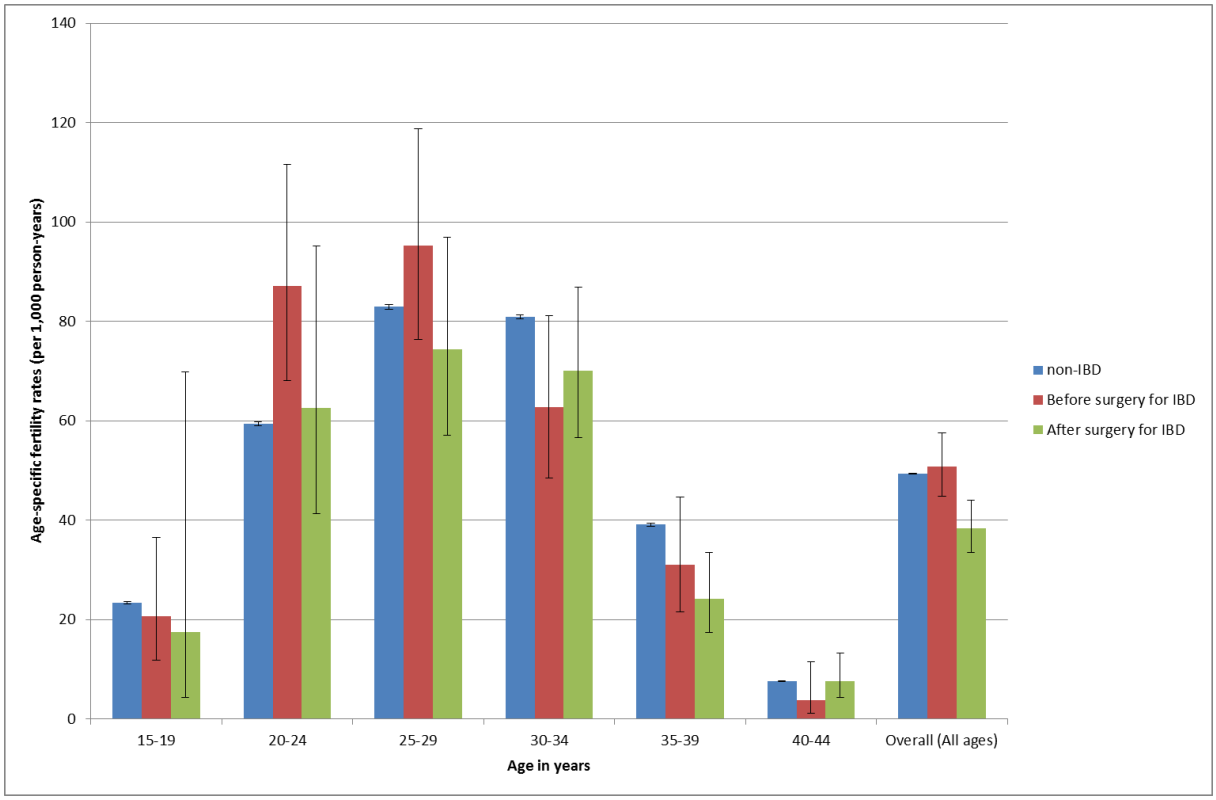



Figure 2. Age-specific fertility rates (per 1,000 person-years) for women with IBD with bowel surgery (N=1,618) compared to women without IBD (N=2,131,864)