**Incidence and prevalence of paediatric inflammatory bowel disease continues to increase in the south of England**

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JJA and RMB conceived the article. FMB, CB, TAC, AB and NAA helped with data collection. JJA performed statistical analyses and wrote the paper. All authors commented on the paper and approved it prior to submission.

Conflicts of interest

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**Abstract**

Objective- The incidence of paediatric inflammatory bowel disease (IBD) has been increasing over 25-years, however contemporary trends are not established and the impact of COVID-19 on case rates is unclear.

Methods- Data from Southampton Children’s hospital prospective IBD database were retrieved for 2002-2021. Incidence rates were calculated based on referral area populations and temporal trends analysed. Disease prevalence for those aged <18 years was calculated for 2017-2021. Monoclonal prescriptions were reported

Results- 1150 patients were included, mean age at diagnosis- 12.63 years, 40.5% female. 704 patients had Crohn’s disease (61.2%), 385 had ulcerative colitis (33.5%), and 61 had IBD unclassified (5.3%).

Overall IBD incidence increased, β= 0.843, p=3 x 10-6, driven by Crohn’s disease, β= 0.732, p=0.00024 and ulcerative colitis, β= 0.816, p=0.000011. There was no change in IBDU incidence, β= 0.230, p=0.33.

From 2002-2021, 51 patients were diagnosed <6 years of age, 160 patients aged 6 to <10 years and 939 patients aged 10 to <18 years of age. Increased incidence was observed in patients aged 10 to <18 years of age (β= 0.888, p=1.8 x 10-7). There was no significant change in incidence of IBD in <6 years (β= 0.124, p=0.57), or 6 to <10 years (β= 0.146, p=0.54).

IBD prevalence increased by an average of 1.71%/year from 2017-2021, β= 0.979, p=0.004. The number of new monoclonal prescriptions increased from 6 in 2007 to 111 in 2021.

Conclusions- IBD incidence continues to increase in Southern England. Compounding prevalence and increased monoclonal usage has implications for service provision.

Key words: IBD; Crohn’s disease; Ulcerative colitis; incidence; prevalence; paediatric

What is known

* Incidence of paediatric inflammatory bowel disease (IBD) has been increasing over the last 20-years
* Worldwide IBD prevalence has also increased, however children account for only a small number of the total prevalent cases globally

What is new

* Incidence of IBD in those aged <18 years continues to increase and is now at the highest reported level in England
* Prevalence is calculated for the first time in an English cohort and demonstrates increases year-on-year since 2017
* Use of biologic therapy has increased dramatically, even when accounting for increased disease incidence

**Introduction**

Paediatric inflammatory bowel disease (IBD) incidence has been increasing over the last 20 years1. Whilst all subtypes of IBD appear to be increasing, the main driver of higher incidence in those aged <18 years of age is Crohn’s disease2. Whilst multiple studies have detailed a rapid increase in ‘Western’ counties, emerging economies and areas of the world with historically low rate of disease, such as Asia and Africa, there are fewer studies reporting prevalence of IBD in childhood and a lack of up-to-date information on the impact of the COVID-19 pandemic on diagnostic rates1.

There are numerous reports of the impact of the pandemic on routine healthcare3,4. Updated incidence rates are important to assess the impact of reduced endoscopy capacity and to plan paediatric gastroenterology services during the recovery. There is additional interest in the differences between areas of high disease incidence, with parts of Canada reporting increased case numbers of very early onset IBD (VEOIBD) patients, contrasting with no reported change in parts of northern Europe5,6.

Prevalence of IBD in children has not previously been reported in England1. Interesting data from Scotland has pointed to only 1.5% of all IBD cases being in those aged <18 years, however overall incidence rates across all age groups were around 40/100,000/year, which are not dissimilar to incidence rates in children ages 10-18 years 1,7,8. The compounding prevalence of IBD in adult populations will also be reflected, to a lesser extent, in paediatrics. Whereas incidence of adult-onset IBD appears to have reached a plateau, over the last 25 years there has been a widely reported doubling of incidence in paediatric-onset disease7,9. This will have significant knock-on effects for healthcare planning in both paediatric diagnostic services and ongoing adult care, following transition.

This study aimed to update incidence in a well-established population and report prevalence of IBD for the first time in a region of England. Additionally, we report incident use of monoclonal therapy with this cohort in the context of increasing disease incidence.

**Methods**

Patients diagnosed from 1st January 2002 until the 31st of December 2021 were identified from the prospectively held clinical database at Southampton Children’s Hospital9. Age of diagnosis, disease subtype, gender and prescriptions of monoclonal antibody therapy were retrieved.

Ethical approval

This study was classified as a quality improvement study and received approval from the divisional lead at University Hospital Southampton.

At risk population estimation

The referral area for the Wessex IBD service, based at Southampton Children’s Hospital has remained stable for the last 5 years. At risk population was derived from office of national statistics data, based on the population of postcodes, and Channel Islands authorities, covered by the clinical referral network, accounting for change in population and population structure over the study period, as previously described2,9. The referral network covers 12 regional hospitals including Portsmouth, Poole, Salisbury, Winchester, Dorchester, Guildford, Frimley Park, Chichester, Basingstoke, Jersey, Guernsey, and the Isle of Wight. Southampton is the tertiary referral centre for this area, caring for all patients diagnosed within this referral network.

Additionally, we estimated specific populations corresponding to commonly used definitions of disease age of onset, <6 years (VEOIBD), 6 to <10 years (early onset IBD) and 10 to <18 years (paediatric onset IBD) using United Kingdom census data from 2011, reflecting the mid time point in our cohort10.

Incidence and prevalence estimation

Standardised incidence was calculated per 100,000 of at-risk population for each year of study, 2002-2021. We estimated prevalence of disease in the 5 years from 2017-2021. The IBD database at Southampton Children’s Hospital holds records from 1999 but was only systematically and prospectively entered from 2002. To ensure any patients aged <3 years who were diagnosed between 1999 and 2001, and could therefore be under 18 years of age in 2017-19, were included we manually cross-checked electronic paediatric gastroenterology clinic lists and identified no additional patients.

To assess prevalence, we ascertained the number of patients under the care of the paediatric gastroenterology service for each year (2017-21) study based on all patients transitioning to adult care before their 18th birthday11,12. Patients attend joint clinic between the age of 17 and 18 years and it is not possible to list the precise age for transition of individual patients. Any patient aged <18 years at any point during a study year were included in the prevalence calculation for that year.

Incidence of monoclonal therapy prescriptions

We extracted the numbers of patients starting on monoclonal therapy in each year of study from prescriptions records. Routine prescribing of monoclonal therapy for IBD patients has occurred since 2007 at Southampton Children’s Hospital and this was treated as the first year to calculate incidence. Monoclonal therapy included were infliximab, adalimumab, vedolizumab and ustekinumab, alongside any biosimilars (infliximab, adalimumab). To determine whether monoclonal antibody prescriptions and new patients started on monoclonal therapy were increasing in relation to incidence, we calculated the number of monoclonal prescriptions, and new patients started on monoclonal therapy, as a ratio to the number of incident cases per year. Any medication switch (monoclonal to monoclonal) was counted as a new prescription.

Analysis

Subclassification of patient characteristics (gender and age of diagnosis) was performed. We compared differences in mean incidence rates of Crohn’s disease and ulcerative colitis for male *vs* female patients by ꭓ2 test. Statistical analysis of incidence trends was conducted by linear regression (SPSS v25). We analysed potential differences in mean age at diagnosis through ANOVA. Temporal trends in disease prevalence were analysed over the 5-year period by average annual percentage change.

**Results**

1150 patients were included across the 20-year study period. The mean age at diagnosis was 12.63 years, 466 patients were female (40.5%). 704 had a diagnosis of Crohn’s disease (61.2%), 385 had a diagnosis of ulcerative colitis (30.4%), and 61 had a diagnosis of IBD unclassified (5.3%). There were no differences in age at diagnosis over the 20-year period as assessed by ANOVA, F=1.437 p=0.101. Table 1.

Male predominance of Crohn’s disease but not ulcerative colitis

Crohn’s disease was more common in male (n=452, 64.2%) compared to female (n=252) patients, which was not reflected in ulcerative colitis- male (n=196, 50.9%) and female (n=189) patients when considering ulcerative colitis, p=1.9 x 10-5.

Incidence of paediatric IBD continues to increase

Overall IBD incidence increased over time, β= 0.843, p=3 x 10-6. This was driven by increasing Crohn’s disease, β= 0.732, p=0.00024 and increasing ulcerative colitis, β= 0.816, p=0.000011. There was no change in the incidence of IBDU over the study, β= 0.230, p=0.33. Figure 1.

Older children are the main driver of increased incidence but there was no change in incidence of very early onset IBD

Over the 20-year study period 51 patients were diagnosed <6 years of age, VEOIBD (range 0.68-5.97 years), 160 patients with early onset IBD, EOIBD (aged 6 to <10 years) and the remaining patients were aged 10 to <18 years of age. We analysed trends in incidence for the different age groups. There was no significant change in incidence of VEOIBD or EOIBD, β= 0.124, p=0.57 and β= 0.146, p=0.54. Incidence increased in the overall cohort was driven by patients aged 10 to <18 years of age β= 0.888, p=1.8 x 10-7. Figure 2.

Prevalence of disease increased over last 5 years

Prevalence increased from 2017-2021, by an average of 1.71% per year, β= 0.979, p=0.004. In 2017 the prevalence was 50.7/100,000, increasing to 51.9/100,000 (2018), 52.9/100,000 (2019), 54.8/100,000 (2020), 57.5/100,000 (2021). Absolute patient numbers increased from 327 in 2017 to 377 in 2021.

Incidence of monoclonal antibody therapy use

The number of patients on monoclonal therapy at Southampton Children’s Hospital increased from 2007 to 2021. The absolute number of new monoclonal prescriptions, including inter and intra-class switches increased year on year since 2007. The number of new patients started on monoclonal therapy, excluding the switches, also increased year on year from 5 patients in 2007 to 82 patients in 2021. Table 1. In 2021 there were 166 patients on monoclonal therapy, reflecting a biological therapy prevalence of 44% in these patients.

The ratio of incident cases per year, to new monoclonal prescriptions, fell significantly from 2007 to 2021, Pearson correlation coefficient (PCC) -0.748, p = 0.001. Similarly, the ratio of incident cases to new patients on monoclonal therapy also fell, PCC -0.749, p = 0.001. Figure 3.

**Discussion**

These data present an update from a well-defined cohort demonstrating continued rises in IBD incidence in the South of England. Additionally, we show this increase is driven by patients aged >10 years of age, with no statistically significant changes in incidence for patients ages <6 years or <10 years at diagnosis. For the first time we present data confirming the increase in prevalence in this cohort.

A recently published systematic review on the epidemiology of paediatric IBD conclusively demonstrated increasing incidence across over 100 studies1. Whilst the number of studies reporting trends in disease prevalence were significantly lower, the 7 datasets able to show this all confirmed increased prevalence, in the populations that were studied. Despite this evidence, contemporary data demonstrating trends in incidence during the COVID-19 pandemic is still required. Rather than demonstrating a reduction in the diagnosis of IBD during the COVID-19 pandemic we report the highest incidence figures for the Wessex region to date. Interestingly, whilst COVID-19 impacted on diagnostic services early in the pandemic, this has now returned to normal 4. Locally, registration of patients remained consistent throughout the pandemic.

We report prevalence trends from English data for the first time, which are concordant with international reports. An unanswered question on the increasing paediatric IBD incidence centres on the role of genetics within these patients, which is presumed to have the highest heritability of disease13,14. No population level genetic drift to increased IBD susceptibility would have occurred within the 20 years, meaning incidence change must be due to environmental factors on a genetic risk background. It may be that the increasing Westernisation of diet, or an increasingly aseptic upbringing, is unearthing a widespread genetic predisposition with multiple different disease aetiologies15.

There continues to be differences in global incidence trends within paediatric IBD, notably within the incidence of VEOIBD. North American data from Ontario has consistently shown an increase in the disease incidence in those aged <6 years at diagnosis, whereas data from our study demonstrate no change in incidence over the last 20 years5. Similarly, we present a predominance of male Crohn’s disease patients, driving the increase in incidence, whereas Japanese data shows higher rates of ulcerative colitis16. Paediatric incidence continues to contrast to adult data when considering the predominantly affected gender and disease subtype, with UK-wide adult data showing higher numbers of affected women and high rates of ulcerative colitis compared to Crohn’s disease17,18. The underlying differences in disease phenotype, and prevalence, between different age groups and geographical regions is likely to have an underlying genetic determinant, coupled with different environmental exposures19.

Monoclonal antibody therapy has become a mainstay of treatment for patients with IBD and we report increased use year on year. Prevalence estimates for monoclonal use in paediatric cohorts are difficult to ascertain, but previous data from our group reported a peak prevalence of anti-TNF use of 27.11% in 201712. Our most recent estimate of monoclonal prevalence within our cohort is 44%, demonstrating a continued increase in incident prescription and maintenance on these medicines. With recent ECCO/ESPGHAN guidelines indicating a preference for top-down therapy in moderate-severe disease and as vedolizumab and ustekinumab become increasingly available as first-line medicines there may be a further increase in monoclonal therapy use20.

These data have important implications for resourcing paediatric IBD services. Additionally, whilst prevalence is increasing within the paediatric age bracket, the compounding prevalence within those aged >18 years will be significantly higher, as demonstrated through recently published data from Scotland where estimated prevalence will exceed 1% within 10 years7. Increased staffing, diagnostic endoscopy provision and monoclonal delivery within paediatric settings will be required with increase in patient numbers. Further to this, ensuring patients who are diagnosed at young ages are treated efficiently and effectively will have lifelong economic and health benefits, at a personal and population level21,22.

This study has several strengths, we build on previously published data with a robust methodology for estimating at-risk population and capturing incident cases. Data capture and diagnostic pathways have remained consistent within the region despite the COVID-19 pandemic. However, there are some limitations, the prevalence data are limited to the last 5-years of study due to lack of routine collation of cases before 2002. Despite this we present the first reported incidence of disease in England and report robust data on monoclonal therapy use. We were unable to include additional clinical data, such as Porto classification, additional treatments or co-morbidities, or indication for monoclonal therapy, as these have not been prospectively collated within our electronic IBD database for the entire study period.

Conclusions

These contemporary data show a continued increase in paediatric IBD incidence in the South of England. For the first time we demonstrate a statistically significant increase in IBD prevalence within the Wessex cohort and report increased incident monoclonal therapy prescriptions. These data have continued relevance for future service provision in paediatric and adult gastroenterology departments.

**Tables and figures**

Figure 1- Incidence of paediatric inflammatory bowel disease over 20 years (2002-2021), including incidence of Crohn’s disease, ulcerative colitis and inflammatory bowel disease unclassified.

Figure 2- Incidence of paediatric inflammatory bowel disease over 20 years (2002-2021), stratified by age of onset- very early onset IBD (VEOIBD), early onset IBD (EOIBD) and paediatric onset IBD.

Figure 3- Ratio of new diagnosis of paediatric inflammatory bowel disease to new monoclonal antibody therapy prescriptions and patients newly prescribed monoclonal antibody therapy, by year of study

Table 1- Mean age at diagnosis (in years), number of new monoclonal prescriptions and number of patients newly prescribed monoclonal antibody therapy, by year of diagnosis

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