Adult height in patients with childhood-onset inflammatory bowel disease: a nationwide population-based cohort study

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Summary

Background: Growth retardation is well described in childhood-onset inflammatory bowel disease (IBD).

Aims: To study if childhood-onset IBD is associated with reduced final adult height.

Methods: We identified 4201 individuals diagnosed with childhood-onset IBD 1990-2014 (Crohn's disease: n = 1640; ulcerative colitis: n = 2201 and IBD-unclassified = 360) in the Swedish National Patient Register.

Results: Patients with IBD attained a lower adult height compared to reference individuals (adjusted mean height difference [AMHD] −0.9 cm [95% CI −1.1 to −0.7]) and to their healthy siblings (AMHD −0.8 cm [−1.0 to −0.6]). Patients with Crohn's disease (CD) were slightly shorter than patients with ulcerative colitis (UC; −1.3 cm vs −0.6 cm). Lower adult height was more often seen in patients with pre-pubertal disease onset (AMHD −1.6 cm [-2.0 to −1.2]), and in patients with a more severe disease course (AMHD −1.9 cm, [−2.4 to −1.4]). Some 5.0% of CD and 4.3% of UC patients were classified as growth retarded vs 2.5% of matched reference individuals (OR 2.42 [95% CI 1.85-3.17] and 1.74 [1.36-2.22] respectively).

Conclusion: Patients with childhood-onset IBD on average attain a slightly lower adult height than their healthy peers. Adult height was more reduced in patients with pre-pubertal onset of disease and in those with a more severe disease course.
1 | INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease characterised by inflammation in the gastrointestinal tract with diverse clinical presentation and prognosis. Traditionally, IBD is divided into three subtypes: ulcerative colitis (UC), Crohn’s disease (CD) and IBD-unclassified. Globally rising rates of paediatric IBD have been demonstrated during recent decades.

Linear growth impairment and pubertal delay are well-known complications in patients with childhood-onset IBD. Both features have been observed more often in patients with CD than UC. The aetiology of growth impairment in IBD is multifactorial. Undernourishment and direct effects of pro-inflammatory cytokines seem to be important explanatory factors. Most therapies that decrease inflammation and improve nutrition seem to have a positive impact on growth. However, corticosteroid therapy has a negative impact on growth velocity although the association with persistent growth reduction in children with IBD might rather be explained by the drug being a marker of more severe and persistent disease activity.

Whether or not the growth delay frequently seen in children with IBD also leads to shorter final height in adult age has been investigated before, but previous studies suffer from a number of limitations; small number of patients, restriction to referral centres with highly selected study populations, study periods that do not represent current paediatric care and no adjustment for parental height (Table S1). Moreover, comparisons between these studies have been difficult as different definitions of growth retardation have been used (Table S2). According to some of these studies, mostly from tertiary centres, a substantial proportion of childhood-onset IBD patients (19-31%) will end up shorter. Other, mostly population based, studies suggest that although a large proportion of children with IBD may have subnormal growth during childhood, the attained adult height is only reduced in a small subset of patients with CD (but not in patients with UC or IBD-U). In a recently published large national population-based study from Israel, the authors did not find any overall significant difference in mean height between conscripts for military service with or without IBD (even though height was measured at age 17 years). The fact that previous studies have not adjusted for parental height is an important limitation since this is the strongest predictor of adult height also in patients with childhood-onset IBD. We therefore performed a nationwide population-based study to test our hypothesis that patients with childhood-onset IBD attain a lower adult height than their disease-free peers and siblings.

2 | METHODS

2.1 | Study design

Using a cohort study design, we compared attained final height in adult age between individuals with childhood-onset IBD and matched general population reference individuals without IBD. In

![Figure 1: Inclusion and exclusion individuals with childhood-onset inflammatory bowel disease 1990-2014](image.png)
sub-analyses, we also compared childhood-onset IBD patients with their IBD-free siblings.

### 2.2 Setting and data sources

In Sweden, patients with childhood-onset IBD are treated by pediatric gastroenterologists until the age of 18 years while adult IBD patients are followed up by gastroenterologists. Sweden is a high-income country with publicly funded healthcare including both in-patient and out-patient care as well as medications available at low cost for all residents. We used the personal identity number, as assigned to all Swedish residents, to link data from national and virtually complete administrative and clinical registers on demography and morbidity. These registers allow for prospective assessment of the complete IBD population, independent of IBD severity or place of residence. Swedish in-patient care has been registered in the National Inpatient Register with nationwide full coverage since 1987 and specialist (nonprimary) out-patient care was included since 2001.

To obtain height data, we used the Nationwide Passport Register provided by the Swedish Police Authority using information for all individuals in the Swedish population with a passport issued after 1991. A passport application must be made in person. During the application process an individual’s height is either measured by the police or self-reported.

### 2.3 Study population

#### 2.3.1 IBD patients

In order to restrict the study population to incident cases of IBD, we identified all individuals in Sweden with a first-time diagnosis of IBD in the Swedish patient register (in-patient care or nonprimary out-patient care) from 1 January 1990 to 31 May 2014 using relevant ICD-codes (Table S3). We identified patients who had ≥2 diagnostic listings of IBD recorded by a physician on two separate occasions before the 18th birthday for women and the 20th birthday for men. At the time of diagnosis, patients were categorised as UC, CD or IBD-unclassified (IBD-U) according to the first two diagnostic codes. All stratified analyses of final height were based on this initial diagnostic classification. The date of the first IBD code was regarded as the date of IBD diagnosis.

For the description of the study population at the time point of adult height measurement, categorisation of IBD into subtypes was based on all available information at the 18th (women) or 20th (men) birthday. Because different IBD diagnoses might be documented during a patient’s medical history, we classified patients with a mix of codes for UC, CD or indeterminate colitis during follow-up as IBD-U. Moreover, patients who only shifted between UC and CD (and vice versa) but who had been diagnosed with only UC or CD over the past 5 years were classified as UC or CD. Finally, patients who had a diagnostic or procedure code typical of CD (Table S4) were classified as CD. The directions of reclassifications during the IBD disease course have been described previously.

#### 2.3.2 Matched general population reference individuals

For each IBD patient, we randomly selected up to 10 IBD-free individuals from the Swedish Total Population Register, matched for sex, age, calendar year and place of residency.

#### 2.3.3 IBD-free siblings

We used the multi-generation register to identify all biological parents and siblings to IBD patients (excluding half-siblings). We identified 3452 IBD patients (82% of the entire study population with IBD) with at least one sibling and compared the final attained adult height between siblings according to IBD status.

### 2.4 Subgroup analyses

Patients were categorised according to age at diagnosis and expected pubertal status at IBD onset. Patients diagnosed before 6 years of age were categorised as very early onset IBD. Males diagnosed between 6 and 12 years of age and females diagnosed between 6 and 10 years of age were categorised as pre-pubertal. Males diagnosed after 12 years of age and females diagnosed after 10 years of age were categorised as pubertal.

For analyses stratified by different disease phenotypes, we used all information available between the date of the first IBD diagnosis and the date when final adult height was supposed to be attained (in women the 18th and in men the 20th birthday). We defined extra-intestinal manifestations in skin, eyes or joints and primary sclerosing cholangitis at any time during follow-up through the corresponding diagnostic codes in ICD-9 and ICD-10, as listed in Table S5. In-patient data regarding IBD-related surgery was available during the whole study period, and out-patient surgery since 1997. Procedures were coded using the sixth version of the Swedish procedure codes before 1997 and the NOMESCO (The Nordic Medico-Statistical Committee) Classification of Surgical Procedures from 1997 and are listed in Tables S4 and S6. Healthcare utilisation during follow-up was used as one of the proxies for IBD severity. IBD-related hospitalisations were defined as in-patient periods with IBD as the main diagnosis.

The Swedish Prescribed Drug Register started on July 1, 2005 and provides information about all dispensed drug prescriptions nationally. We analysed IBD patients’ exposure to systemic corticosteroids (ATC-codes in Table S7). All analyses regarding drug exposure were restricted to IBD patients diagnosed after the start of the Prescribed Drug Register (1 July 2005).
2.4.1 Parental information, including target height

Height measurements of biological parents were obtained from the Nationwide Passport Register to allow for adjustment of target height, which was calculated as previously described and adapted to means, standard deviations and correlations of adult heights of available parents. We calculated target height taking into account two important correlations: the correlation for assortative mating and the parent-offspring correlation.

We used the longitudinal integrated Database for Health insurance and labour Market Study (LISA) and the Total Population Register to define family situation and parental educational level for the parents of the study population at the time of IBD onset.

2.5 Outcome measures

2.5.1 Main outcome measure

Our main outcome was attained final height at any time after start of adulthood, defined as 18 years for women and 20 years for men. To illustrate that individuals in Sweden do not gain height after age 18 years for women and 20 years for men, the association between height and age in a random sample of 50 000 height measurements available in the Swedish population register is presented in Figure 1. Final heights <100 or >240 cm for men and >225 cm for women were considered likely to be erroneous and were treated as missing.

2.5.2 Secondary outcome measure

A secondary outcome measure was the presence of any growth retardation at the same time point. Growth retardation was defined as >8.5 cm of height below the target height (roughly equal to >1.5 SD).

2.6 Statistical methods

We used linear regression to analyse the effect of IBD on final adult height adjusting for target height and the matching variables sex, age, index date and place of residency. We used logistic regression with robust standard errors for the binary outcome of height less than 100 cm below the target height. In this setting, the odds ratios are good approximations of relative risks. We performed the analyses with height as the dependent variable and IBD as the independent variable, adjusting for parental height and the matching variables. We also analysed stratum-specific estimates of how UC, CD, IBD-U, different ages of onset, or different proxies for disease severity (eg phenotypes or treatment) were associated with the final adult height.

In another model, we restricted the analysis to IBD cases living in families with more than one child and used fixed effects linear regression for the height outcome and generalised linear mixed models with random intercepts for the outcome of growth retardation, both conditional on sibling group. Sibling analyses were adjusted for sex and year of height measurement. Subgroups with small sample sizes (less than 60 cases and reference individuals combined) were not analysed.

Statistical analyses were performed using R statistical software (version 3.3.1, R Foundation for Statistical Computing) and the lme4 package.

3 RESULTS

3.1 Background data

We identified 7579 patients who were diagnosed with IBD during childhood or adolescence. Out of them, 1905 did not reach adulthood during the study period and were excluded (Figure 1). Among the remaining 5674 patients, 1473 patients did not have a valid adult height measurement and they were more often (65%) diagnosed during the end of the study period (2006-2014, which is expected, since they had less time to get a passport after reaching adulthood) but had similar patient- and disease characteristics to those with valid adult height measurements (Tables 1 and 2). The majority of the IBD patients were boys (59%) and the mean age at first IBD diagnosis was 15 years (Table 1). Of the 4201 IBD patients with valid adult height measurements, 1900 (45%) were classified as UC, 1,812 (43%) as CD and 489 (12%) as IBD-U when they had attained the final height (Table 2). Before adult height measurement, 592 (14%) of the IBD patients had been treated with intra-abdominal surgery (Table 2). Out of the 1193 children and adolescents diagnosed with IBD after 1 July 2005 (when The Swedish Prescribed Drug Register started), the majority (81%) were exposed to systemic corticosteroids during childhood (Table 2). The distribution of target height of patients with different IBD subtypes did not differ from matched reference individuals stratified by sex (Figure S9).

3.2 Final adult height

The mean final adult height was 166.1 cm in women and 180.4 cm in men with childhood-onset IBD compared to 166.9 cm in females and 181.0 cm in males among the matched reference individuals (Figure 2). The adjusted analysis (Figure 3 and Table 3) demonstrated that patients with IBD, as compared with the reference individuals, attained a statistically significant shorter final height in adult age (adjusted mean height difference (AMHD) −0.9 cm, 95% confidence interval (CI) −1.1 to −0.7). The association with lower adult mean height was stronger in patients with CD (AMHD −1.3 cm, 95% CI −1.6 to −1.0) than in patients with UC (AMHD −0.6 cm, 95% CI −0.9 to −0.4; Table 3 and Figure 3). Differences in adult mean heights were more prominent in patients with IBD onset before puberty (AMHD −1.6 cm, 95% CI −2.0 to −1.2) than in patients with onset during or after puberty (AMHD −0.8 cm, 95% CI −0.9 to −0.6) and in the subsets of patients who were exposed to bowel surgery (AMHD −1.9 cm, 95% CI −2.4 to −1.4), perianal
surgery (AMHD −1.5 cm, 95% CI −2.3 to −0.7), or in-patient treatment for >30 days listing IBD as the main diagnosis (AMHD −1.4 cm, 95% CI −1.8 to −1.0) during childhood.

When restricting the analyses to siblings (Table 3 and Figure 3), the association of IBD with shorter mean adult height remained (AMHD −0.8 cm, 95% CI −1.0 to −0.6). The more prominent differences in final adult height in patients with CD, pre-pubertal onset or exposed to surgery or in-patient treatment remained also in the sibling restricted comparisons. We found no statistically significant association of very early onset IBD with reduced mean height in adult age, but the number of patients was small (n = 46, AMHD −1.6, 95% CI −3.3 to 0.1).

In a subanalysis, we examined the association of final height with IBD separately for children with disease onset from 1990 to 2001 or 2002 to 2013 (Table S10). A larger proportion of children with disease onset before 2002 had disease onset in pre-pubertal age compared with those diagnosed in 2002 or later (since those with pre-pubertal IBD onset did not attain adult final height before end of study). When we analysed the two subsets stratified by age at diagnosis, height deficit in patients diagnosed with IBD before 2002 was similar with those diagnosed in 2002 and later (AMHD −1.0 cm, 95% CI −1.3 to −0.8 vs AMHD −0.8 cm, 95% CI −1.0 to −0.6).

3.3 | Growth retardation

Patients with IBD had an increased risk of growth retardation compared with general population reference individuals (odds ratio, OR 1.99, 95% CI 1.68-2.37) (Figure 4 and Table S11). Some 4.6% of all IBD patients, 5.0% of CD and 4.3% of UC patients were classified as growth retarded compared to 2.5% of the matched general population reference individuals.

The OR of growth retardation was higher for patients with CD (OR 2.42, 95% CI 1.85-3.17) than for those with UC (OR 1.74, 95% CI 1.36-2.22). Higher relative risks for growth retardation was observed in the subsets of IBD patients with pre-pubertal disease onset (OR 3.88, 95% CI 2.72-5.52) and in those patients who were exposed to bowel surgery (OR 2.95, 95% CI 1.94-4.50) during childhood or in-patient treatment for >30 days (OR 2.75, 95% CI 1.94-3.89). The number of growth retarded IBD patients with siblings was too few to allow confirmation of many of the ORs derived from the population reference comparisons.

4 | DISCUSSION

4.1 | Main findings

In this nationwide register-based study, we found that patients with childhood-onset IBD had a doubled risk of being classified as growth retarded and attained statistically significant lower adult height, compared with general population reference individuals and non-IBD siblings. The negative impact of disease was modest, as patients with childhood-onset IBD attained a mean final height only one cm below that of their healthy peers and siblings (Table 3). However, our study

### Table 1: Characteristics at the time of diagnosis/matching of patients with childhood-inflammatory bowel disease (IBD) and their matched general population reference individuals and siblings. N (%) if not otherwise stated

|                      | Inflammatory bowel disease | Ulcerative colitis | Crohn's disease | IBD-Unclassified | IBD-missing height | Reference individuals | Siblings |
|----------------------|---------------------------|--------------------|-----------------|------------------|-------------------|----------------------|----------|
| **Total**            | 4201 (100)                | 2201 (52)          | 1640 (39)       | 360 (9)          | 1473              | 56361                | 5370     |
| **Girls**            | 1702 (41)                 | 870 (40)           | 682 (42)        | 150 (42)         | 443 (30)          | 21312 (38)          | 2314 (43)|
| **Boys**             | 2499 (59)                 | 1331 (60)          | 958 (58)        | 210 (58)         | 1030 (70)         | 35049 (62)          | 3056 (57)|
| **Age of IBD onset** |                           |                    |                 |                  |                   |                      |          |
| Mean (SD) years      | 15 (3)                    | 15 (3)             | 15 (3)          | 15 (3)           | 15 (3)            | 15 (3)              | 15 (3)  |
| Median (IQR) years   | 16 (13-17)                | 16 (13-17)         | 16 (13-17)      | 16 (13-17)       | 16 (13-17)        | 16 (13-17)          | 15 (13-17)|
| <6 y                 | 46 (1)                    | 38 (2)             | 6 (0)           | 2 (1)            | 32 (2)            | 779 (1)             | 66 (1)   |
| <10 y                | 277 (7)                   | 177 (8)            | 73 (4)          | 27 (8)           | 147 (10)          | 4221 (7)            | 373 (7)  |
| **Year of IBD onset**|                         |                    |                 |                  |                   |                      |          |
| 2006-2014            | 1059 (25)                 | 540 (25)           | 413 (25)        | 106 (29)         | 955 (65)          | 20373 (36)          | 1271 (24)|
| 1998-2005            | 2129 (51)                 | 1095 (50)          | 871 (53)        | 163 (45)         | 430 (29)          | 25398 (45)          | 2830 (53)|
| 1990-1997            | 1013 (24)                 | 566 (26)           | 356 (22)        | 91 (25)          | 88 (6)           | 10926 (19)          | 1269 (24)|
| **Source of attained final adult height**|                   |                    |                 |                  |                   |                      |          |
| Passport register    | 4200 (100)                | 2201 (100)         | 1640 (100)      | 359 (100)        | —                | 41606 (100)         | 4177 (100)|
| Conscription dataa   | 1 (0)                     | 0 (0)              | 0 (0)           | 1 (0)            | —                | 15 (0)              | 2 (0)    |
| Missing height       | 0 (0)                     | 0 (0)              | 0 (0)           | 0 (0)            | 1473 (100)        | 14736 (26)          | 1190 (22)|

a All biological IBD-free whole siblings to patients with IBD.

b Conscription was only mandatory for boys during parts of the study period, and typically took place at 17-18 y of age (ie before the age defined as when final height was attained).
also showed that patients with disease onset before puberty or a disease course characterised by markers associated with severe disease (eg bowel surgery or longer in-patient treatment) attained lower mean final heights and had distinctively increased risks of growth retardation.

### Findings compared to earlier studies

There are few studies on the final height attained during adult age in patients with childhood-onset IBD (Table S1). Most of these studies are small and relatively old and were not population-based.18,19,21 Our study demonstrated that childhood-onset IBD patients seem to attain a statistically significant lower adult height compared to matched reference individuals similar to other studies.23,25 However, in contrast to most of these studies we found that the height difference between childhood-onset of IBD patients and their healthy peers and siblings was very modest and that only a small fraction of the patients were growth retarded when they reached adult age.

A much cited British study from 2006 by Sawczenko reported that as much as one in five of the 123 studied childhood-onset CD patients attained a final height at the adult age that was classified as growth retarded.23 Using a similar definition, we found that less than 5% of CD patients were growth retarded as adults (and the attributable fraction to disease was only 2.5%; Table S1). Aside from the slight difference in definition, the large discrepancy between the two studies might to some extent be explained by the development of paediatric IBD care over the years. Most of the patients in the British study were evaluated in young adult age during the 1990s, while the large majority of the children in our study were diagnosed after the introduction of anti-TNF therapy (1998). Moreover, in the British study, patients were recruited from a tertiary referral centre in London and as much as 27% of the children were reported to have jejunal disease involvement at diagnosis, which questions the generalisability of the study. In a contemporary population-based study from Stockholm only 1% of the childhood-onset CD patients were reported to present with jejunal disease.41 Hence, the over-representation of patients with more severe phenotypes in the British referral centre study might even be the main reason for the large differences in risk estimates compared to our population-based study.

There are to our knowledge only a small number of population-based studies that have evaluated attained height in adult or near adult age in patients with childhood-onset IBD.20,25,26 A recently published study from Israel did not find any significant difference in mean height between conscripts for military service of both sexes with IBD (n = 2372) or without IBD (n = 1 144 213) in late adolescent age (median 17.1 years).26 These study results are somewhat surprising as several studies have demonstrated that a large proportion of childhood-onset IBD patients have a delayed pubertal onset and the prevalence of growth retardation decreases as they approach adulthood.18,20 Although the proportion of IBD children who have to face a delayed

| TABLE 2 | Patient characteristics at the time of final height and disease course characteristics from diagnosis of childhood-onset inflammatory bowel disease (IBD) to 18 y for women and 20 y for men. N(%) if not otherwise stated. |
|-----------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Inflammatory bowel disease** | **Ulcerative colitis** | **Crohn’s disease** | **IBD-Unclassified** | **IBD missing height** |
| Total | 4201 (100) | 1900 (45) | 1812 (43) | 489 (12) | 1473 |
| **Age of disease onset** | | | | | |
| Very early onset (<6 y) | 46 (1) | 29 (2) | 11 (1) | 6 (1) | 32 (2) |
| Pre-pubertal | 659 (16) | 314 (17) | 284 (16) | 61 (12) | 289 (20) |
| Pubertal | 3496 (83) | 1557 (82) | 1517 (84) | 422 (86) | 1152 (78) |
| **Phenotypes during follow up** | | | | | |
| Extra intestinal manifestations | 125 (3) | 41 (2) | 67 (4) | 17 (3) | 72 (5) |
| Primary sclerosing cholangitis | 217 (5) | 141 (7) | 37 (2) | 39 (8) | 74 (5) |
| Colitis | 1673 (40) | 862 (45) | 634 (35) | 177 (36) | 609 (41) |
| **IBD Surgery** | | | | | |
| Bowel surgery | 592 (14) | 160 (8) | 410 (23) | 22 (4) | 143 (10) |
| Perianal surgery | 249 (6) | 28 (1) | 220 (12) | 1 (0) | 107 (7) |
| **IBD hospitalisation** | | | | | |
| No IBD in-patient days | 717 (17) | 348 (18) | 263 (15) | 106 (22) | 418 (28) |
| >0 to ≤30 IBD in-patient days | 2479 (59) | 1109 (58) | 1063 (59) | 307 (63) | 826 (56) |
| >30 IBD in-patient days | 840 (20) | 337 (18) | 436 (24) | 67 (14) | 208 (14) |
| **Systemic corticosteroid use before adulthood** | | | | | |
| None | 228 (19) | 97 (19) | 94 (20) | 37 (18) | 175 (17) |
| Some | 965 (81) | 413 (81) | 378 (80) | 174 (82) | 835 (83) |

*a* Girls/boys diagnosed between 6 and 10/6 and 12 years of age were considered pre-pubertal. Later onset was considered pubertal.

*b* The Swedish Prescribed Drug Register started on 1 July 2005 and analyses of drug exposures are restricted to incident patients after that date.
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4.3 | Mechanistic explanations

This is the first population-based study showing that patients with childhood-onset UC also seem to attain a slightly shorter final height in adult age. Most growth studies on children with IBD have reported that growth retardation, delayed puberty and reduced height during adult age is restricted to patients with CD.20,21,25 Our significant findings could to some extent be explained by the much larger number of patients in our study, but it should be noticed that the strength of the negative association with final adult height was only slightly weaker for UC (AMHD −0.6 cm) than for CD (AMHD −1.3 cm). Evidence suggests that growth retardation in children with CD is caused by malnutrition and direct effects of proinflammatory cytokines. In an experimental study by Ballinger on rats with induced colitis, it was estimated that 60% of linear growth failure could be attributed to undernutrition and that inflammation did account for the remaining deficit.21 It is possible that the increasing use of nutritional therapy in children with CD has diminished the negative impact of malnutrition and that growth retardation today is predominantly caused by inflammatory cytokines as documented earlier in experimental studies.43 It might be speculated that persistent inflammation in the modern IBD treatment era is a stronger predictor for decreased final height during adult age than the phenotype of IBD.

It is possible that the only modest negative association of childhood-onset IBD with reduced final height in our study could be explained by improved IBD care during recent decades; more frequent use of nutritional therapy, steroid restricted regimens, immunomodulatory drugs and minimally invasive surgery. However, it is also possible that earlier studies have overinflated the negative effect of IBD as many of these studies have also included heights of patients in late adolescence who might not have reached their final adult height. We took into consideration that many children with IBD can have a late pubertal onset and therefore do not reach final height until well into the adult age.18,20 Consequently, we defined final height as the height measurement at or after 18 years of age for women and at or after 20 years of age for men.

4.4 | Strengths and limitations

To our knowledge, this is the largest population-based study on the association of childhood-onset IBD with final height in the adult age. Our study is almost twice as large as the second largest study and 20 times larger than the second largest population-based study (Table S1). We retrieved our patients from the Swedish Patient Register with nationwide follow-up since 1987 and follow-up of IBD patients, regardless of disease severity and place of residence, thus minimising the risk of misclassification and selection bias. We were able to compare final heights in IBD patients with IBD-free reference individuals, matched

FIGURE 2 Violin plots of the observed density of final height, mirrored about the centre axis, comparing patients with different childhood-onset inflammatory bowel disease subtypes (IBD) and matched reference individuals by sex. Points represent the median and lines the quartiles. The mean final height was 166.1 cm in women with IBD compared to 166.9 cm in women without IBD, and 180.4 cm in men with IBD compared to 181.0 cm in men without IBD. Matched reference individuals are 10 times more than IBD patients. It is therefore more likely that individuals with extremely short heights (eg Silver-Russel syndrome, Turner syndrome, achondroplasia, etc.) are included in that group.

| Height (cm) | No IBD | UC | CD | IBD-U |
|------------|-------|----|----|------|
|           |       |    |    |      |
| Girls     |       |    |    |      |
| IBD-U     |       |    |    |      |
| CD        |       |    |    |      |
| UC        |       |    |    |      |
| No IBD    |       |    |    |      |
| Boys      |       |    |    |      |

Girls: The mean final height was 166.1 cm in women with IBD compared to 166.9 cm in women without IBD, and 180.4 cm in men with IBD compared to 181.0 cm in men without IBD. Matched reference individuals are 10 times more than IBD patients. It is therefore more likely that individuals with extremely short heights (eg Silver-Russel syndrome, Turner syndrome, achondroplasia, etc.) are included in that group.
by sex, age, birth year and place of residence, from the Total Population Register which has virtually complete coverage of the Swedish population, thus addressing potential confounders and ensuring good generalisability. The high statistical power in our study allowed not only for precise risk estimations but also for important subanalyses.

Through the personal identification number, we were able to link nationwide registry data. Linkage to The Multi-Generation Register provided means to identify all biological parents to the IBD patients and thus allowed us to adjust for parental height. Through the Multi-Generation Register we could also identify all siblings to the IBD patients which allowed us to make confirmative sibling analyses. To our knowledge, this is the first study to compare the final height of IBD patients to their IBD-free siblings. By comparing whole siblings with discordant exposures and outcomes, genetic and environmental factors are kept more constant (compared to matched reference individuals), which therefore decreases the effect of unmeasured confounders. The consistent results in the general population analyses and in the sibling analyses provided robust support to the conclusions of our study.

**FIGURE 3** Adjusted mean differences (cm) and 95% confidence intervals in final height in patients diagnosed with childhood-onset inflammatory bowel disease (IBD) and matched general population reference individuals or siblings. Numbers in figure represent patients in each strata. The association of childhood-onset IBD with final height was analysed in linear regression models. All analyses were adjusted for matching variables (age, sex, year and place of residence) and for birth order, number of siblings, parental height, parental education. Sibling analyses were stratified within each family and adjusted for sex and year. The sibling models used a linear fixed effects model, with fixed effects for each sibling group. The analyses were restricted to whole siblings. Medication analyses were restricted to incident patients since the start of the prescribed drug register in 2005.
We calculated target height taking into account the correlation for assortative mating and the parent-offspring correlation which allowed us to make more accurate estimates compared to other studies. While our results were robust, we acknowledge a number of limitations. Our capacity to characterise patients according to disease severity was limited as we had no data on biochemical analyses, endoscopic examinations or clinical grading scales. We did not have any individual information on pubertal staging or growth velocity why we could not study the association of pubertal delay or growth impairment with final height. Furthermore, the Prescribed Drug Register was only started during the later part of the study period and did not fully cover infusion biologics which is why we did not estimate the impact of biologics for final height. However, the observation that the final adult height was similar in children diagnosed during the first half of the study period (before 2002) to those diagnosed in the later part (2002 and later) argues against a strong effect of the introduction of anti-TNF.

We used the Nationwide Passport Register to gather information about final adult height. These data are partly based on self-reported height. But since such misclassification could be expected to be non-differential, it is very unlikely that this has had any major influence on the study results. A large proportion of the IBD patients (26%) did not have valid height measurement in adult age but similar proportions

### TABLE 3

|                           | N     | Crude mean difference in cm (95% CI) | Adjusted mean difference in cm (95% CI) | N with siblings | Sibling-compared mean difference in cm (95% CI) |
|---------------------------|-------|--------------------------------------|----------------------------------------|-----------------|-----------------------------------------------|
| **No IBD**                | 41,725| Ref                                  | Ref                                    | 5370            | Ref                                           |
| **Diagnosis**             |       |                                      |                                        |                 |                                               |
| Inflammatory bowel disease| 4201  | -0.9 (-1.0 to -0.7)                  | -0.9 (-1.1 to -0.7)                    | 3452            | -0.8 (-1.0 to -0.6)                           |
| Ulcerative colitis        | 2201  | -0.6 (-0.8 to -0.4)                  | -0.6 (-0.9 to -0.4)                    | 1800            | -0.7 (-1.0 to -0.4)                           |
| Crohn’s disease           | 1640  | -1.2 (-1.5 to -0.9)                  | -1.3 (-1.6 to -1.0)                    | 1367            | -1.1 (-1.4 to -0.7)                           |
| IBD-Unclassified          | 360   | -0.9 (-1.6 to -0.3)                  | -0.9 (-1.5 to -0.3)                    | 285             | -0.1 (-0.9 to 0.7)                            |
| **Age of disease onset**  |       |                                      |                                        |                 |                                               |
| Very early onset          | 46    | -1.8 (-3.6 to -0.1)                  | -1.6 (-3.3 to 0.1)                     | 44              | -2.3 (-4.6 to 0.1)                            |
| Pre-pubertal              | 659   | -1.5 (-2.0 to -1.1)                  | -1.6 (-2.0 to -1.2)                    | 584             | -1.7 (-2.4 to -1.1)                           |
| Pubertal                  | 3496  | -0.7 (-0.9 to -0.5)                  | -0.8 (-0.9 to -0.6)                    | 2824            | -0.6 (-0.9 to -0.4)                           |
| **Phenotype during follow-up** |     |                                      |                                        |                 |                                               |
| Extra intestinal manifestations | 125 | -1.0 (-2.1 to 0.1)                  | -0.9 (-2.0 to 0.2)                     | 100             | -1.1 (-2.5 to 0.3)                            |
| Primary sclerosing choilangitis | 217 | -0.7 (-1.5 to 0.0)                  | -0.8 (-1.5 to -0.0)                    | 192             | -0.2 (-1.2 to 0.8)                            |
| Colitis                   | 1673  | -0.9 (-1.2 to -0.6)                  | -0.9 (-1.2 to -0.7)                    | 1407            | -0.9 (-1.3 to -0.6)                           |
| **IBD surgery**           |       |                                      |                                        |                 |                                               |
| Bowel surgery             | 592   | -1.9 (-2.3 to -1.4)                  | -1.9 (-2.4 to -1.4)                    | 471             | -1.5 (-2.1 to -0.9)                           |
| Perianal surgery          | 249   | -1.5 (-2.2 to -0.7)                  | -1.5 (-2.3 to -0.7)                    | 193             | -1.8 (-2.8 to -0.8)                           |
| **IBD hospitalisation**   |       |                                      |                                        |                 |                                               |
| No IBD in-patient days   | 717   | -0.3 (-0.7 to 0.1)                  | -0.3 (-0.7 to 0.1)                     | 587             | 0.2 (-0.4 to 0.8)                             |
| >0 to ≤30 IBD in-patient days | 2479 | -0.8 (-1.1 to -0.6)                  | -0.9 (-1.1 to -0.7)                    | 2048            | -1.1 (-1.3 to -0.8)                           |
| >30 IBD in-patient days  | 840   | -1.4 (-1.8 to -1.0)                  | -1.4 (-1.8 to -1.0)                    | 684             | -0.8 (-1.3 to -0.3)                           |
| **Cumulative systemic corticosteroid use before adulthood** |     |                                      |                                        |                 |                                               |
| None                      | 228   | -1.0 (-1.7 to -0.2)                  | -1.2 (-1.9 to -0.4)                    | 175             | -0.6 (-1.7 to 0.5)                            |
| Some                      | 965   | -0.8 (-1.2 to -0.5)                  | -0.8 (-1.2 to -0.5)                    | 775             | -0.6 (-1.1 to -0.0)                           |

a The association of childhood-onset IBD with final height was analysed in linear regression models. Analyses were adjusted for matching factors (sex, age, year and place of residence) and for birth order, number of siblings, parental height and parental education.

b Sibling analyses were stratified within each family and adjusted for sex and year. A linear fixed effects model with fixed effects for each sibling group was used. The analysis was restricted to whole siblings.
with missing height were also seen among siblings (22%) and the general population reference individuals (26%). When IBD patients' missing adult height data were compared with those with valid adult height data, similar patient- and disease characteristics were seen in both groups.

It should also be noticed that Sweden is a high-income country with universal access to healthcare and medication for all children. Our results are therefore not necessarily generalisable to IBD populations in countries with very limited access to healthcare for all or some socioeconomic strata.

### FIGURE 4

Odds ratio of growth retardation in childhood-onset inflammatory bowel disease (IBD) compared with matched general population reference individuals and siblings. Numbers in figure represent number of patients and proportion of these patients classified as growth retarded in each strata. Defined as final height >8.5 cm below target height (ie approximately 1.5 SDs). The risk in patients with childhood-onset IBD of growth retardation was analysed in logistic regression models with robust standard errors and with adjustment for birth order, number of siblings and parental education. The sibling models used a generalised linear mixed effects model, with random intercepts for each sibling group, and adjustment for sex, birth order and year. The analysis was restricted to whole siblings. Odds ratio is not reported if total sample size in the group including reference individuals is less than 60. Medication analyses were restricted to incident patients since the start of the prescribed drug register in 2005.

### 4.5 Clinical implications

Our findings should be reassuring to most children with IBD and their parents, as the large majority of childhood-onset IBD patients seem to attain a final adult height close to their full growth potential. Nevertheless, our study also shows that childhood-onset IBD seems to have a stronger negative impact on final height in patients with disease onset before puberty and in subsets of patients characterised by markers of a more severe disease course. Despite the improvement in nutritional, medical and surgical care...
of patients with childhood-onset IBD, some children still face a disabling disease course and will attain a markedly reduced final height in adult age.

5 | CONCLUSIONS

Patients with childhood-onset IBD on average attained a statistically significant lower final adult height and were more often growth retarded than general population reference individuals or the IBD patients’ healthy siblings. However, most patients with childhood-onset IBD seemed to attain a final adult height that was only modestly lower than that of their healthy peers and siblings. Subsets of patients characterised by markers of severe inflammation had a stronger association with reduced final adult height, which calls for improved care for these children.

ACKNOWLEDGEMENT

Declaration of personal interests: Olén has been PI on projects at Karolinska Institutet partly financed by investigator-initiated grants from Janssen, Ferring, Takeda and Pfizer. None of those studies have any relation to the present study. Karolinska Institutet has received fees for Olén’s lectures and participation on advisory boards from Janssen, Ferring, Takeda and Pfizer regarding topics not related to the present study. Asking reports grants from AbbVie, Bristol-Myers Squibb, Lilly, Merck, Pfizer, Roche, Samsung Bioepis and UCB, mainly in the context of a national safety monitoring programme for immunomodulators in rheumatology (ARTIS). Ludvigsson coordinates a study unrelated to the present study on behalf of the Swedish IBD Quality Register (SWIBREG). That study has received funding from Janssen. Authors not named here have disclosed no conflicts of interest.

AUTHORSHIP

Guarantor of the article: Natalia Mouratidou.

Author contributions: Olén, Malmborg: Study concept; Olén: Acquisition of data; Sachs, Olén: Analysis; Mouratidou, Malmborg, Olén: Drafting of the manuscript. All co-authors involved in the study design; interpretation of results and critical revision of the manuscript for important intellectual content.

STUDY REPORT GUIDELINE

The study is presented according to the recommendation by the STROBE statement on how to report observational studies in epidemiology. STROBE checklist for cohort studies was used.

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33. How to cite this article: Mouratidou N, Malmborg P, Sachs MC, et al. Adult height in patients with childhood-onset inflammatory bowel disease: a nationwide population-based cohort study. *Aliment Pharmacol Ther*. 2020;51:789–800. https://doi.org/10.1111/apt.15667

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