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Predicting Outcomes in Pediatric Crohn's Disease for Management Optimization: Systematic Review and Consensus Statements from PIBD-Ahead Program

Short Title: Predicting Outcomes in Pediatric CD

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Abbreviations

aHR	adjusted hazard ratio
ANCA	antineutrophil cytoplasmic antibodies
ASCA	anti-*Saccharomyces cerevisiae* antibodies
B2	stricturing behavior
B3	internal penetrating behavior
B2/B3	stricturing and/or internal penetrating behavior
BMD	bone mineral density
BMI	body mass index
CD	Crohn's disease
CI	confidence intervals
GI	gastrointestinal
HR	hazard ratio
IBD	inflammatory bowel disease
Ig	immunoglobulin
OR	odds ratio
pANCA	perinuclear antineutrophil cytoplasmic antibody
PCDAI	Pediatric CD Activity Index
PGA	Physician Global Assessment
PIBD	pediatric inflammatory bowel disease
SC	steering committee
SD	standard deviation
SDS	standard deviation scores
TNF	tumor necrosis factor
UC	ulcerative colitis

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ABSTRACT

BACKGROUND AND AIMS: A better understanding of prognostic factors within the heterogeneous spectrum of pediatric Crohn's disease (CD) should improve patient management and reduce complications. We aimed to identify evidence-based predictors of outcomes with the goal of optimizing individual patient management.

METHODS: A survey of 202 experts in pediatric CD identified and prioritized adverse outcomes to be avoided. A systematic review of the literature with meta-analysis, when possible, was performed to identify clinical studies that investigated predictors of these outcomes. Multiple national and international face-to-face meetings were held to draft consensus statements based on the published evidence.

RESULTS: Consensus was reached on 27 statements regarding prognostic factors for surgery, complications, chronically active pediatric CD, and hospitalization. Prognostic factors for surgery included CD diagnosis during adolescence, growth impairment, *NOD2/CARD15* polymorphisms, disease behavior, and positive anti-*Saccharomyces cerevisiae* antibodies (ASCA) status. Isolated colonic disease was associated with fewer surgeries. Older age at presentation, small bowel disease, serology (ASCA, antiflagellin, and OmpC), *NOD2/CARD15* polymorphisms, perianal disease, and ethnicity were risk factors for penetrating (B3) and/or stenotic disease (B2). Male sex, young age at onset, small bowel disease, more active disease, and diagnostic delay may be associated with growth impairment. Malnutrition and higher disease activity were associated with reduced bone density.

CONCLUSIONS: These evidence-based consensus statements offer insight into predictors of poor outcomes in pediatric CD and are valuable when developing treatment algorithms and

planning future studies. Targeted longitudinal studies are needed to further characterize

prognostic factors in pediatric CD and to evaluate the impact of treatment algorithms tailored

to individual patient risk.

Keywords: ASCA, serology, NOD2/CARD15, growth impairment, polymorphism, prognostic

factors, structuring or penetrating disease, complications.

INTRODUCTION

Pediatric-onset Crohn's disease (CD) is heterogeneous. Beyond stricturing (B2), internal penetrating (B3) disease and need for surgery, complications in pediatric CD include perianal fistulizing disease, linear growth impairment, malnutrition, pubertal delay, and decreased bone mineral density (BMD). Early intensified treatment may reduce the development of complications[1] and thus identification of prognostic factors in pediatric CD can improve patient management.

The international pediatric inflammatory bowel disease (PIBD) "Ahead program" (PIBD-Ahead) aimed to identify evidence-based predictors of poor outcomes in PIBD, with the goal of optimally individualizing management based on knowledge of risk factors. The results specific to CD are herein reported.

METHODS

Scope and Purpose

PIBD-Ahead encompassed several stages, aiming to systematically reach international consensus on the predictors of poor outcomes in PIBD. First, a steering committee (SC), consisting of two co-chairs (AMG and DT) and 15 members (the other authors), determined which undesirable outcomes were most important to predict. Pediatric gastroenterologists involved in the care of children with inflammatory bowel disease (IBD) internationally were approached through the online PIBD network (https://www.pibd-net.org/) or personal contacts to participate in a survey, wherein scale-based questions were used to determine disease outcomes, which, if preventable with biologics, would mandate early interventions.

Thereafter, a systematic review of the literature was performed to identify studies examining predictors of the chosen outcomes. Pooling of the effects between predictors and key outcomes was performed using meta-analysis, where possible. Finally, following a series of national and international meetings with large groups of PIBD experts, consensus statements were formulated based on the evidence.

Literature Inclusion Criteria

We considered randomized controlled trials, prospective and retrospective cohort studies, and case-control studies that examined pediatric patients (as defined by individual studies) for inclusion in the review. Studies that reported on any patient or disease factor as a predictor of at least one of the outcomes of interest identified below were eligible. Studies were excluded if they were not available in English (for feasibility reasons and given that most major journals make articles available in English), or if they were available only in abstract form given that data from abstracts and full manuscripts can be inconsistent.

Systematic Search and Meta-analysis

In a face-to-face meeting in Prague (May 2017), the scope of the literature review was finalized by the SC. Databases searched included Cochrane, EMBASE, and PubMed from January 1992 to May 2017. Search strings and eligibility criteria were developed specifically for each database (see Supplemental Materials). Additional relevant publications were retrieved based on review of reference lists of included studies and as suggested during the national meetings through discussion with leaders in the field. Bibliographic fellows (MA, AR, EOM, and NC) reviewed all abstracts in duplicate to determine which full texts to retrieve. Full texts were also

reviewed in duplicate (MA, AR, EOM, and NC). At both stages, disagreements were resolved by

consensus with input from one of the principal investigators (AMG, DT).

Data were extracted independently and in duplicate (MA, AR, and EOM) onto standardized

case report forms. Extracted data included the following: study characteristics (design,

single/multicenter, number of participants); participant characteristics (IBD type, age, sex);

outcome(s) and predictor(s) examined (including definitions); and follow-up duration/timing of

outcome assessment. For studies included in meta-analyses, effect estimates, expressed either

as 2x2 tables (number of participants with and without the predictor who experienced the

outcome), odds ratio (OR) and/or hazard ratio (HR), were extracted as well as whether results

were unadjusted or adjusted. Otherwise, studies were reviewed qualitatively for whether they

demonstrated a significant association between a predictor and outcome. Study authors were

not contacted for missing data given the large number of included studies.

Risk of bias was assessed for all studies by a single rater (MA, AR, EOM) using the

Newcastle-Ottawa Scale, as appropriate for observational studies (no randomized controlled

trials were identified). The Newcastle-Ottawa Scale is based on eight factors (total score range

0–9) across three domains, namely selection, comparability, and outcome/exposure. We

defined a high-quality study as a total score of 8–9, moderate quality as 5–7, and low quality as

0–4.

We decided *a priori* that we would attempt to meta-analyze only the most clinically

pertinent and homogeneous outcomes, which, by consensus, we identified to be surgery and

B2/B3 complications. Studies examining these outcomes were not pooled if they were felt to be

too clinically heterogeneous. For dichotomous outcomes, the pooled measure of treatment

effect was OR and, for time to event outcomes, the pooled measure of treatment effect was HR, both expressed with 95% confidence intervals (CI). Results were pooled using random effects in all cases, as we expected at least some clinical heterogeneity between studies. This was accomplished using inverse variance and DerSimonian and Laird methods. Statistical heterogeneity was evaluated across pooled studies using the I^2 statistic. Heterogeneity was also explored graphically by examining outliers in forest plots. ORs and HRs were considered separately and, where both were available, both were presented. Univariate and multivariable effect estimates were also generally considered separately. However, univariate and multivariable effect estimates were pooled if point estimates were similar (provided that adjustment did not substantially alter the association between predictor and outcome) or statistical heterogeneity was low ($I^2 \leq 40\%$).[2] We had planned to assess publication bias graphically using funnel plots, but this was not possible due to insufficient study numbers (<10) per outcome. Analyses were performed using R version 4.0.0.

Consensus Process

The consolidated report and draft statements were reviewed by the SC, and the validity of the statements was discussed at national face-to-face meetings organized by AbbVie in 27 countries, including Argentina, Australia, Austria, Bahrain, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Qatar, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, and the United Kingdom. Comments received during the meetings were considered by the SC during a second face-to-face meeting of the SC in September 2017 in Barcelona, where the statements were finalized.

At the final February 2018 consensus meeting in Vienna, the SC and national representatives (53 participants) voted on the statements. A statement was accepted if ≥80% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1–5 (with 1, 2, and 3 indicating strongly disagree, disagree, and uncertain, respectively). Statements not achieving agreement were further revised and subjected to repeat vote until consensus was reached for all statements. In general, soft wording, such as "may predict", has been used when only one positive study was available or when there was more than one positive study, but also with negative conflicting studies.

RESULTS

The international survey of outcome selection was completed by 202 practicing pediatric gastroenterologists from 33 countries. Based on the survey, the SC concluded that the most important undesirable outcomes to predict in CD could be categorized as disease complications (including B2 and B3 disease), intestinal resection, perianal fistulizing disease, chronically active inflammatory disease, significant growth impairment, and bone disease. B2 and B3 complications and intestinal resection were selected for meta-analysis.

The results of the search are presented in the PRISMA diagram in Supplemental Figure 1. One hundred and one studies were included, of which 42 were included in the quantitative meta-analysis. Study characteristics and risk of bias for studies examining predictor-outcome combinations included in meta-analyses are shown in Table 1 and Table 2, respectively. The equivalent data for studies examining predictor-outcome combinations not included in meta-

analyses are shown in Supplemental Tables 1 and 2. All included studies were observational. Thirty-one studies were high quality, 45 moderate quality, and 25 low quality.

Figure 1 tabulates the final consensus statements. Table 3 presents the extracted numeric data for predictor-outcome pairs included in meta-analyses. Table 4 presents an intuitive summary of each outcome. A summary of the most pertinent literature is provided below each statement (for a full review of each predictor, see Supplemental Materials).

Prognostic Factors for Surgery

Statement 1.1. Diagnosis in adolescence (>13 years of age), compared with younger age, may predict increased risk of bowel surgery within 5 years of diagnosis (94% agreement).

Thirteen studies[3-15] assessed age as a possible predictor of bowel surgery; of these four found older age (>13 years) to be a significant predictor of surgery.[4-7] The largest cohort with significant findings included 989 children aged 0–17 years and found an adjusted OR of 1.12 per 1-year increase in age (95% CI 1.06–1.18, P<.0001).[6]

Statement 1.2. Growth impairment at diagnosis predicts increased risk of bowel surgery (81% agreement).

Five studies evaluated the association of growth impairment with the risk of bowel surgery, of which three showed a significant association.[4, 6, 8, 14, 16] Two meta-analyzable studies revealed a 1.72-fold higher risk for surgery in patients with growth impairment (pooled HR 1.72, 95% CI 1.27–2.33, P=.0004, n=1,438, I^2=0%, Figure 2A).[6, 16] One of the two negative studies had a mixed PIBD cohort rather than CD only.[14]

Statement 1.3. Disease location may predict surgery; isolated colonic disease is associated with fewer surgeries (84% agreement).

Twelve studies evaluated disease location as a predictor for the risk of surgery.[4-10, 16-20] Four meta-analyzable studies showed a significantly lower risk of surgery in patients with isolated colonic disease (pooled HR 0.57, 95% CI 0.43–0.78, P=.0003, n=2,289, I^2=24%, Figure 2B).[5, 6, 10, 16] The pooled unadjusted OR from a smaller analysis of two studies with no heterogeneity further supported this (pooled OR 0.30, 95% CI 0.15–0.58, P=.0003, n=621, I^2=0%, Supplemental Figure 2A).[16, 17] Conversely, this indicates that the presence of small bowel disease (isolated or with colonic disease) increases the risk of surgery. Of the studies that could not be included in the meta-analysis, three reported disease location to not be a significant risk factor.[7-9] Attard et al. found jejunal involvement and disease in the proximal ileum to be associated with an increased surgery risk (unadjusted HR 3.7, P<.03), but upper gastrointestinal (GI) disease and esophageal involvement were not found to be significant risk factors by two other studies.[4, 20]

Statement 1.4. **Inconclusive evidence exists for sex as a predictor for surgery; presence of *NOD2/CARD15* variants, stricturing and/or internal penetrating (B2/B3) phenotype, and positive anti-*Saccharomyces cerevisiae* antibodies (ASCA) status predict surgery; ethnicity and presence of granulomas at diagnosis do not predict surgery** (90% agreement).

Ten studies [5, 6, 9-12, 14, 16, 17, 21] evaluated the association between sex and surgery. Meta-analysis of six studies[5, 6, 9, 11, 16, 17] found no significant risk for sex (pooled OR 0.95, 95% CI 0.73–

1.22, P=.27, n=2,780, I^2=22%, Figure 2C). A smaller analysis of five studies with greater

heterogeneity showed a decreased risk of surgery with male sex but bordered the null (pooled

HR 0.82, 95% CI 0.68–0.99, P=.04, n=4,256, I^2=36%, Supplemental Figure 2B).[6, 10, 12, 16, 21] The

largest study, not included in the meta-analysis, reported male sex to be a significant risk factor

in a mixed IBD cohort.[14] Conversely, Dubinsky et al., also not included in the meta-analysis,

reported an increased risk for females in a multivariable analysis (HR 1.69, 95% CI 1.07–2.17,

P<.009). The two remaining studies did not report a significantly increaed risk for either sex.[10, 12]

Eleven studies evaluated the presence of a *NOD2/CARD15* variant as a predictor of

surgery,[18, 21-30] of which three found a significant association.[26-28] The largest cohort of 186

patients with childhood-onset CD found a higher risk for surgery in those with a 3020insC

mutation (adjusted HR [aHR] 5.83, 95% CI 2.62–12.98, P<.0001).[27] The data from six studies

could be pooled, which resulted in a 2-fold increased risk (pooled OR 2.02, 95% CI 1.23–3.32,

P=.006, n=797, I^2=35%, Figure 2D).[22-26, 28]

Disease behavior was evaluated as a risk factor for surgery in four studies.[5, 8, 10, 16]

Pooled HR of 2.55 for B3 disease behavior (95% CI 0.95–6.88, P=.06, n=1,248, I^2=46.0%, Figure

2E)[5, 10] and a pooled HR of 3.97 (95% CI 1.56–10.10, P=.004, n=1,248, I^2=81.1%, Figure 2F) for B2

disease behavior was found.[5, 10] Rinawi et al. found children with B2/B3 disease to be at

increased risk of surgery (aHR 2.54, 95% CI 1.59–4.05, P<.001).[16]

Five[6, 16, 17, 21, 31] out of eight studies[6, 16, 17, 21, 31-34] evaluating the association between

ASCA status and surgery showed a significant association. The pooled OR for five meta-

analyzable studies was 2.31 (95% CI 1.74–3.06, P<.0001, n=1128, I^2=0, Figure 2G).[16, 17, 21, 31, 32]

The pooled HR for four of these studies also demonstrated a significantly increased risk of surgery (HR 2.59, 95% CI 1.63–4.11, *P*<.0001, n=1033, I^2=0%, Supplemental Figure 2C).[6, 16, 17, 21] Of the three studies without a significant association,[32-34] one included both CD and ulcerative colitis (UC).[33] Ethnicity did not predict the risk of surgery.[5, 6, 9, 35] Presence of granulomas was not associated with the risk of surgery.[6, 16, 36-38]

Prognostic Risk Factors for Complications in Pediatric CD

Statement 2.1. Children who develop CD at an older age may be at increased risk of developing internal penetrating (B3) complications, but not stricturing (B2) disease (94% agreement).

Three studies[18, 39, 40] found no association between age and progression to B2 disease, none of which could be meta-analyzed due to differing methods (univariate vs multivariable Cox regression) and age definitions. Two[39, 40] of four studies,[14, 18, 39, 40] including the RISK study,[40] a large (n=913) prospective inception cohort of pediatric CD, found an association between older age during childhood and increased risk of B3 complications. The RISK study was the only prospective and high-quality study among the four. No association was reported between age and progression to the combined outcome of B2 or B3 complications in four studies.[41-44] Meta-analysis was not possible due to differences in age definitions and differences in the effect estimates used in individual studies.

Statement 2.2. CD patients of Black ethnicity/race are more likely than White patients to develop penetrating (B3) disease (82% agreement).

When pooled, two studies, including the RISK cohort, found non-White children to be at higher risk of progressing to penetrating complications than White children (pooled OR 3.46, 95% CI 1.67–7.17, P=.0009, n=1,020, I^2=0%, Figure 3A).[40, 45] The RISK study compared Black children to White children in a large cohort and adjusted analysis (HR 3.19, 95% CI 1.39-7.31). By comparison, the study by Li et al. examined a small South Asian cohort (n=13) in an unadjusted analysis and did not find a significant association (OR 2.05, 95% CI 0.49-8.53). In a third study including 105 children with inflammatory CD, Black children progressed more rapidly to the combined outcome of B2 or B3 complications (OR 3.48, 95% CI 1.32–9.17, P=.011, n=137).[35] In these studies, follow-up duration ranged from 3 to 10 years.

Statement 2.3. CD patients with small bowel disease (ie, L1 or L3 +/– L4b) have an increased risk of developing stricturing complications (B2) and may be at an increased risk of developing penetrating complications (B3) (85% agreement).

Three studies examined the association between disease location and stricturing complications. Although the RISK study found no association in adjusted analyses for isolated ileal disease (aHR 1.60, 95% CI 0.88–2.91, P=.12),[40] when unadjusted results for any small bowel involvement from this study were pooled with a second study,[46] any small bowel disease was a significant risk factor for B2 behavior (pooled OR 1.93, 95% CI 1.22–3.05, P=.005, n=1,513, I^2=6%, Figure 3B). A smaller (n=36) uncontrolled study found no such association.[11] Four studies reported on disease location and the combined outcome of B2 or B3 complications; three could be meta-analyzed,[43, 44, 46] revealing an increased risk with ileal involvement (isolated ileal or ileocolonic) compared to isolated colonic disease (pooled OR 2.16, 95% CI 1.26–3.71, P=.005,

n=819, I^2=36%, Figure 3C). The fourth study, which could not be meta-analyzed, was retrospective and reported B2/B3 as a composite outcome that also included anti-tumor necrosis factor (TNF) use (HR 1.38, 95% CI 0.63–3.03, *P*=.44).[42] Neither of the two studies to examine disease location and B3 complications found a significant association.[40, 46] They could not be meta-analyzed.

Statement 2.4.1. Antimicrobial serologies predict progression to stricturing (B2) and/or internal penetrating (B3) complications: ASCA positivity predicts progression to internal penetrating (B3) complications and may predict progression to stricturing (B2) complications; a higher ASCA immunoglobulin (Ig) A titer predicts progression to penetrating (B3) complications (94% agreement).

The literature on antimicrobial serology and progression to complicated CD in children is difficult to interpret, given the heterogeneity of tests investigated. Overall, it appears that an association exists, particularly between ASCA positivity and B3 disease. The RISK study identified a trend toward an association between ASCA-IgA and B2 disease in an adjusted survival analysis (aHR 1.69, 95% CI 0.94–3.07).[40] A much smaller and unadjusted analysis identified no association between ASCA positivity and early B2 complications.[11] Furthermore, the RISK study identified a clearly increased risk of B3 complications with ASCA-IgA positivity (aHR 2.68, 95% CI 1.19–6.04), which remained similar in magnitude when pooled with another adjusted study (pooled HR 2.75, 95% CI 1.53–4.97, *P*=.0008, n=1,052, I^2=0%, Figure 3D).[17, 40] The pooled unadjusted OR for these two studies was 4.45 (95% CI 2.43–8.16, *P*<.0001, I^2=0%, Supplemental Figure 2D). A large adjusted study also demonstrated an association between

ASCA-IgA titer and B3 disease (HR 1.20, 95% CI 1.08–1.34, *P*=.0009, n=139).[17] The one study

that did not support an association between ASCA-IgA (positivity or titer) and B3 disease was

substantially smaller and did not employ survival analysis.[34] On the other hand, for ASCA-IgG

positivity, two studies found no association with B3 disease (pooled OR 1.58, 95% CI 0.75–3.36,

P=.231, n=200, I^2=2.7%, Figure 3E).[17, 34] Both studies were individually negative when examining

ASCA-IgG titer as well.

Statement 2.4.2. Antiflagellin (CBir1) positivity predicts progression to stricturing (B2) and/or

internal penetrating (B3) complications; OmpC positivity may predict progression to

stricturing (B2) and/or internal penetrating (B3) complications (94% agreement).

The RISK study observed a strong association between CBir1 positivity and B2 as well as

B3 complications.[40] Similarly, in a longitudinal cohort of 536 children, CBir1 and, separately,

OmpC positivity, both predicted B2 or B3 complications over time.[21]

Statement 2.4.3. Seropositivity for ≥1 microbial serologies predicts progression to stricturing

(B2) and/or internal penetrating (B3) disease; a higher number of positive serologies and

higher titers may confer a greater risk (94% agreement).

The pooled results from two studies support an increased risk of developing B2 or B3

complications with any antimicrobial seropositivity (eg, ASCA, anti-OmpC, or anti-CBir1)

compared with negative status for all serologies (pooled OR 3.20, 95% CI 1.41–7.26, *P*=.0055,

n=703, I^2=0%, Figure 3F).[21, 47]

Statement 2.5. Polymorphisms in the *NOD2/CARD15* gene predict ileal disease location and may predict stricturing (B2) disease, but location is inadequately controlled for (90% agreement).

Twelve studies explored the association between *NOD2* and B2 complications, including nine that could be meta-analyzed, which showed an increased risk of B2 disease (pooled OR 3.10, 95% CI 1.70–5.65, P=.0002, n=1,050, I^2=55%, Figure 3G).[18, 23-29, 48] The three studies that could not be pooled found no association.[40, 49, 50] Since most of these studies did not adjust for disease location, it is unclear whether *NOD2*'s association with B2 disease stems directly from its association with ileal location. A meta-analysis of nine of the 11 studies that assessed the association between *NOD2* and B3 complications revealed no increased risk (pooled OR 1.48, 95% CI 0.78–2.81, P=.23, n=1,050, I^2=48%, Figure 3H).[18, 23-29, 48] The two additional studies that could not be meta-analyzed were also negative.[40, 50]

Statement 2.6. The presence of perianal disease may predict stricturing (B2) and/or internal penetrating (B3) complications (89% agreement).

Two studies yielded conflicting findings on perianal disease as a predictor of B2 or B3 complications.[44, 51] When pooled, although the effect estimate was in the direction of an increased risk of B2/B3 disease in children with perianal disease, this did not achieve statistical significance (pooled OR 1.98, 95% CI 0.51–7.74, P=.32, n=383, I^2=80%, Figure 3I). Notably, there was substantial heterogeneity in this analysis. An administrative database study reported an increased risk of internal fistulae (rectourethral, rectovaginal, or enterovesical) in the setting of perianal disease (OR 3.50, 95% CI 1.98–6.20, n=12,465); although, in the same study, perianal

disease was associated with a decreased risk of entero-enteric fistulae (OR 0.30, 95% CI 0.15–0.63).[14]

Statement 2.7. Sex, family history of IBD, disease activity at baseline, granulomas, upper GI tract involvement, presence of extraintestinal manifestations, and diagnostic delay do not predict disease location, stricturing (B2) and/or internal penetrating (B3) complications (83% agreement).

Sex was not found to predict B2/B3 complications in seven of eight studies examining this association.[11, 41-44, 52, 53] Similarly, family history of IBD (0/3 studies positive),[11, 42, 44] baseline clinical and biochemical disease activity (one study positive,[43] five negative),[11, 41, 42, 44] granulomas (0/6 studies positive),[36-38, 41, 44, 54] extraintestinal manifestations (0/2 studies positive),[42, 44] diagnostic delay (0/1 study positive),[44] and upper GI tract involvement (0/3 studies positive)[41-43] were not associated with progression to complicated CD.

Statement 2.8. Older age at CD onset may be associated with an increased risk of developing perianal disease (97% agreement).

The oldest age group (17–21 years of age) at disease onset of 7,076 patients in the ImproveCareNow Network had a higher rate of perianal disease than younger children (HR 1.13, 95% CI 1.10–1.15).[55] In a second study, including 215 children, older age at diagnosis was also associated with more perianal disease over time.[44] Furthermore, Gupta et al. observed a trend toward more perianal disease in children >5 years of age (vs younger children).[39] In

contrast, children with and without perianal disease did not differ in terms of age in the RISK study.[40]

Statement 2.9. Children and adolescents of Black and South Asian ethnicity with CD are at a greater risk of developing perianal disease (92% agreement).

Black[55] (adjusted OR 2.47, *P*=.017) and South Asian[45] children were at higher risk of developing perianal disease than Caucasian children.

Statement 2.10. Bacterial serology and sex may be associated with the development of perianal disease; genetics, antineutrophil cytoplasmic antibody (ANCA) positivity, anthropometric parameters, disease location, disease behavior, extraintestinal manifestations, diagnostic delay, and disease activity do not predict the development of perianal disease (86% agreement).

ASCA, antilaminaribioside carbohydrate antibodies, antimannobioside carbohydrate antibodies, and anti-L antibodies were associated with the composite outcome of perianal disease or B2/B3 complications in one study.[32] In the RISK cohort, children with perianal disease at diagnosis were more likely to be ASCA IgA/IgG, CBir1, GM-CSF, and OmpC-positive, and the proportion of males was greater among children with perianal disease.[40] However, both these studies examined perianal disease in a cross-sectional manner. Only one[55] of three[44, 53] additional studies found an association between sex and risk of perianal disease. Two of these additional studies[44, 55] examined the development of perianal disease over time, while the other was cross-sectional in nature.[53]

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Overall, genetics (two studies positive,[56, 57] nine negative, including for *NOD2*),[22, 23, 27-29, 49, 50, 58, 59] ANCA positivity (0/2 studies positive),[40, 60] anthropometric parameters (0/3 studies positive),[44, 55, 61] disease location (0/3 studies positive),[40, 44, 55] disease behavior (0/1 study positive),[44] extraintestinal manifestations (0/1 study positive),[44] diagnostic delay (0/1 study positive),[44] and disease activity (0/3 studies positive)[40, 44, 55] did not predict the development of perianal disease over time.

Statement 2.11. Male sex, younger age at disease onset, and isolated small bowel disease may be associated with a greater risk of linear growth impairment (100% agreement).

Although five studies found no association between sex and growth,[4, 62-65] four other large and well-designed studies did observe males to be at higher risk of linear growth impairment.[53 66 67, 68] The studies on age in relation to growth impairment are conflicting. Four found no association,[39, 53, 63, 68] though two were mixed IBD studies.[63, 68] In four additional studies, younger age at diagnosis predicted growth impairment,[4, 62, 65, 67] and a single study observed the opposite.[69] These differences may relate to varying definitions for growth impairment as well as failure to adjust for pubertal status. Three growth-focused studies found small bowel disease (vs colonic location) to be associated with growth impairment,[65, 66, 70] whereas five others of poorer quality did not report this association.[4, 8, 62, 63, 71]

Statement 2.12. More active disease (assessed at baseline or over time) predicts linear growth impairment (92% agreement).

Some studies supported an association between more active disease and poorer growth, though most were cross-sectional rather than truly predictive. Specifically, two studies observed an association between more severe clinical disease and impaired growth,[63, 70] whereas two did not.[8, 62] Four studies found an association between higher erythrocyte sedimentation rate and growth impairment,[68, 69, 72, 73] whereas three found no association between C-reactive protein or albumin and linear growth.[63, 69, 72]

Statement 2.13. Diagnostic delay is a risk factor for linear growth impairment (92% agreement).

Two studies focused on CD found an association between diagnostic delay and impaired growth.[66, 74] Two studies that did not differentiate between CD and UC found no such association.[68, 75]

Statement 2.14. *NOD2/CARD15* polymorphisms may be associated with low weight, and extraintestinal manifestations may be associated with linear growth impairment; pubertal status at disease onset, family history of IBD, ethnicity, gestational age, upper GI tract involvement, oral involvement, granulomas, disease behavior, perianal disease, and presenting symptoms do not predict linear growth impairment (94% agreement).

Three studies examined *NOD2/CARD15* in relation to growth,[26, 29, 70] only one of which was positive, reporting that 50% of children with at least one *NOD2/CARD15* variant were in the lowest weight percentile (<4%) compared with 16% of children without a variant.[26] One study observed an association between extraintestinal manifestations and lower height at last follow-

up,[67] whereas another found no such association in a mixed IBD cohort.[68] Pubertal status at CD diagnosis (0/2 studies positive),[62, 71] family history of IBD (0/3 studies positive),[8, 62, 68] ethnicity (0/3 studies positive),[35, 62, 68] gestational age (0/1 study positive),[8] presence of granuloma (0/1 study positive),[38] perianal disease (0/2 studies positive),[4, 76] disease behavior (0/2 studies positive),[8, 62] specific IBD symptoms (0/1 study positive),[53] upper GI tract location (0/6 studies positive),[4, 62, 63, 67, 70, 77] and oral involvement (0/1 study positive)[78] were not associated with growth impairment.

Statement 2.15. Low height, weight, and body mass index predict reduced BMD (98% agreement).

All 10 studies that examined nutritional status/anthropometrics in relation to reduced BMD reported an association with either lower weight or lower height.[29, 79-87] For weight, 9/9 studies were positive,[29, 79-85, 87] and for height, 5/8 studies were positive,[79, 80, 83, 85, 88] while three were negative.[29, 81, 87] Importantly, most studies reporting on height were cross-sectional.

Statement 2.16. Higher clinical disease activity (assessed by Pediatric CD Activity Index [PCDAI]) at baseline and over time may predict reduced BMD (98% agreement).

Ten studies investigated disease activity in relation to bone outcomes, with heterogeneous results, possibly since several were cross-sectional.[29, 79, 81-83, 85, 87, 89-91] Five studies found an association between clinical disease activity and BMD,[82, 89 29, 81, 85] whereas five other studies did not,[79, 83, 87, 90, 91] including two prospective studies.[87, 90]

Statement 2.17. Sex, disease location, disease behavior, extraintestinal manifestations, granulomas, and perianal disease do not predict BMD (84% agreement).

No association has been shown between sex and bone health in seven pediatric studies,[29, 53, 79, 80, 83, 85, 92] while two showed contradictory associations.[88, 89] Disease location (0/3 studies positive),[29, 83, 87] behavior (0/1 study positive),[29] extraintestinal manifestations (0/2 studies positive),[29, 85] presence of granuloma (0/1 study positive),[83] and perianal disease (0/1 study positive)[85] were not predictive of bone outcomes.

Prognostic Risk Factors for Chronically Active Inflammatory Pediatric CD

Statement 3.1. ASCA positivity may predict the need for more intensive therapy (89% agreement).

Three studies examined ASCA positivity as a predictor for intensified therapy,[11, 33, 93] two of which identified a positive association.[33, 93]

Statement 3.2. Microscopic ileocolonic involvement at diagnosis may be associated with subsequent macroscopic ileocolonic disease (98% agreement).

One study of 212 children reported on microscopic ileocolonic involvement as an independent predictor of the subsequent development of macroscopic disease.[44] The need for an immunomodulator or anti-TNF within the first year, and number of flares and hospitalizations were associated with disease-extent progression, but only microscopic ileocolonic involvement remained significant in the multivariable analysis (HR 4.32, 95% CI 1.93–9.67).

Statement 3.3. Disease activity and disease behavior (ie, B2 and/or B3), but not age and sex, may predict more intensive therapies or a poor response to therapies; there is no strong evidence for a predictive value of ethnicity (83% agreement).

Three studies examined the association between PCDAI at diagnosis and subsequent treatment,[94-96] of which only one (n=240) reported an association with the need for immunomodulators by 1 year.[96] One of two studies found an association between B3 behavior and use of anti-TNF.[57, 95]

Only 2/10 studies reported an association between age and intensified treatment.[3, 11, 13, 39, 64, 97-101] The first, a prospective registry of 1,928 children, found that younger children (1–5 years) received corticosteroids and methotrexate more often than older children, but with a similar rate for biologics.[100] The other study found that younger children (0–5 years) received steroids more often but with a similar rate for immunomodulators or biologics.[3]

Sex was not found to predict intensified therapy in four studies.[64, 97, 99, 101] One study reported an association between male sex and better response to steroids, but this was not maintained over time.[97]

Two studies evaluated ethnicity and intensified therapy. Although positive, they did not separate CD from UC patients, and each assessed different ethnicities (South Asian[45] or Black[35] vs White).

Statement 3.4. No strong evidence exists to identify predictive factors of future disease activity or disease severity (81% agreement).

Of three studies investigating predictive factors of disease severity in pediatric CD,[8, 60, 65] two identified an association.[8, 65] The first study found an association between ileal/ileocolonic location and PCDAI or Physician Global Assessment.[8] In the second, the presence of TNF 308G/A genetic polymorphism was associated with a trend for severe disease, as represented by hospitalizations, surgery, and need of steroids or anti-TNF.[65] No association was found between ANCA serology and disease course.[60]

Statement 3.5. No strong evidence exists for predictors of disease relapse and the number of relapses (98% agreement).

Four[13, 23, 34, 102] of six[77, 78] studies reported significant predictors for disease relapse (as defined by clinical activity score), including ASCA IgA positivity,[34] younger age at disease onset,[13] ATG16L1 risk allele homozygosity,[23] and a polymorphonuclear neutrophil CD64 index >1.0 (vs <1.0).[102] Gasparetto et al. found children aged 5–10 years at diagnosis to relapse more frequently than children with disease onset at 11–16 years of age (mean relapse per patient per year 1.4 ± 0.2 standard deviation [SD] vs 0.85 ± 0.1 SD, respectively; OR 1.2, 95% CI 1.01–1.65). However, owing to study limitations of sample size, retrospective design, and heterogeneity in the results, these findings do not represent strong evidence for predictors of occurrence or number of disease relapses.

Statement 3.6. Stricturing and/or internal penetrating (B2/B3) phenotype and the presence of granulomas and increased visceral adipose tissue may predict hospitalizations; small bowel

involvement, *TNF* polymorphisms, *NOD2* variants, and age do not predict hospitalization (88%
agreement).

Predictors for hospitalizations were investigated in seven studies, all with different
predictors.[13, 19, 29, 37, 65, 100, 103] Age,[13, 100] proximal bowel involvement,[19] and the presence of
NOD2 variants[29] or TNF polymorphisms[65] were not associated with hospitalization. One study
found that patients with granulomas were more likely to be hospitalized (HR 1.43, 95% CI 1.0–
2.0), whereas they did not display an increased risk for bowel resections or flares.[37] Uko et al.
found increased visceral adipose tissue to be associated with hospitalizations (OR 1.9, 95% CI
1.2–3.4, *P*=.01) in a retrospective study.[103] Although no studies evaluated the association
between B2/B3 disease and hospitalization, the association of B2/B3 disease with surgery as
mentioned in statement 1.4 reflects this association. This was supported by a recent study
showing that B2/B3 disease was associated with an increased risk for hospitalization (HR 1.5, 95%
CI 1.1–2.1, *P*=.016).[104]

IMPLICATIONS FOR PRACTICE

The concept of severe CD in children is recognized to encompass not only progression to
intestinal complications requiring extensive or repeated resection, but also chronically active
disabling disease, which remains inflammatory. This may lead to other age-specific outcomes
such as growth impairment and reduced bone density, which can further adversely impact
children emotionally during a particularly sensitive time in their adolescence. Physicians
intuitively risk-stratify patients soon after diagnosis and make treatment recommendations
aiming to prevent these undesirable outcomes. However, evidence-based tools to stratify

patient risk and tailor treatment selection accordingly are needed. This is particularly salient as there is good evidence of better outcomes resulting from earlier effective medical intervention in pediatric CD. This was shown in the RISK cohort, for example, in which early anti-TNFα treatment within 3 months of diagnosis was associated with improved clinical and growth outcomes at 1 year.[1]

This project represents the most comprehensive review of the available literature to this date in an attempt to develop evidence-based guidance on risk factors for severe pediatric CD. As such, it represents an important and contemporary addition to the literature. The involvement of a large number of pediatric IBD experts from around the world and the consensus approach are important strengths of this undertaking. There are, however, a number of limitations. Firstly, despite the comprehensive search strategy, there was a paucity of large, prospective, pediatric-specific CD studies for several of the predictor-outcome pairs. Meta-analyses, in general, included a fairly small number of studies. In some cases, studies pooled CD and UC populations. This highlights the need for additional large and rigorously performed longitudinal studies in pediatric CD, both to further characterize prognostic factors and to evaluate the benefits of treatment algorithms that tailor treatment based on risk stratification informed by these risk factors. Additional limitations include heterogeneity of included studies. Sources of heterogeneity included definitions of predictors and outcomes, with growth being one example of a factor for which various definitions were used, as well as differences in the types of effect measures reported by individual studies. While we made efforts to pool studies when justified based on similar definitions and types of effect measures, substantial

heterogeneity remained for some analyses. In addition, we excluded non-English texts and

were unable to contact study authors.

In summary, the present consensus statements offer clinicians evidence of associations

between baseline characteristics and outcomes in children with CD. Antimicrobial antibodies

may be associated with stricturing or internal penetrating CD and surgery, but biomarkers of

equally disabling chronic inflammatory colonic disease or progressive perianal fistulizing disease

are direly needed. As in adults, precision medicine is not yet a reality in pediatric CD.

Nonetheless, the associations summarized and meta-analyzed through PIBD-Ahead provide

some guidance to the physician making initial treatment decisions for the individual child.

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Figure Legends

Figure 1. Summary of Consensus Recommendations for the Management of Inflammatory Disease

Figure 2. Forest plots for predictors of surgery in pediatric CD: A – poor growth; B – isolated colonic disease; C – male sex; D – NOD2/CARD15 variant; E – B3 behavior; F – B2 behavior; G – ASCA positivity

Figure 3. Forest plots for predictors of B2/B3 complications in pediatric CD: A – non-White ethnicity/race as a predictor of B3 complications; B – small bowel disease (±colonic) as a predictor of B2 complications; C – small bowel disease (±colonic) as a predictor of B2 or B3 complications; D – ASCA-IgA positivity as a predictor of B3 complications; E – ASCA-IgG positivity as a predictor of B3 complications; F – antimicrobial seropositivity as a predictor of B2 or B3 complications; G – NOD2 polymorphisms as a predictor of B2 complications; H – NOD2 polymorphisms as a predictor of B3 complications; I – perianal disease as a predictor of B2 or B3 complications

Table Legends

Table 1. Characteristics of Studies Examining Predictor-Outcome Combinations Included in Meta-Analysis

Table 2. Risk of Bias for Studies Examining Outcomes Included in Meta-Analysis

Table 3. Findings from Individual Studies Examining Predictor-Outcome Combinations Included in Meta-Analysis

Table 4. Summary of Outcomes and Respective Predictors in Pediatric CD

Supplemental Figures

Supplemental Figure 1. PRISMA diagram

Supplemental Figure 2. Additional forest plots for predictors of surgery and B2/B3 complications in pediatric CD: A – isolated colonic disease as a predictor of surgery; B – male sex as a predictor of surgery; C – ASCA positivity as a predictor of surgery; D – ASCA-IgA positivity as a predictor of B3 complications

Supplemental Tables

Supplemental Table 1. Characteristics of Studies Examining Predictor-Outcome Combinations Not Included in Meta-Analysis

Supplemental Table 2. Risk of Bias Studies Examining Predictor-Outcome Combinations Not Included in Meta-Analysis

Table 1. Characteristics of Studies Examining Predictor-Outcome Combinations Included in Meta-Analysis

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Aloi (2013)	Retrospective, single center	36 pediatric CD Mean 14.7 (±4.12) y, 67% M	Disease location ASCA+ (IgA or IgG)	B2 (early stricture within 3 months of diagnosis) Surgery Intensified treatment	Mean 2.48 (SD 4.12) y
Ammoury (2011)	Retrospective, single center	81 pediatric CD Mean 11.6 (range 4–18) y, 63% M	Esophageal involvement	Surgery	Mean 3.5 y (range 6 mo–10 y)
Amre (2006)	Retrospective, single center	139 pediatric CD Mean 11.2 (SD 3.4) y, 52% M	Sex Disease location (SB only, colon only, SB and LB) ASCA (IgA, IgG, positivity, and titer)	B3 (fistula or abscess) Surgery (ileocecal resection, perianal abscess drainage ± fistulectomy)	Mean 5.8 (SD 3) y
Attard (2004)	Retrospective, single center	134 pediatric CD Mean 12.0 (SEM 1.2) y	Jejunoileitis	Surgery Hospitalization	N/A
Birimberg-Schwartz (2016)	Retrospective, multicenter	406 pediatric IBD (mixed cohort) Mean 10.5 (SD 3.9) y, 54% M	Serology (ASCA, pANCA)	Surgery Intensified treatment (biologic or calcineurin inhibitor)	Median 2.8 (IQR 1.6-4.2) y
Chhaya (2015)	Retrospective, multicenter	1595 pediatric CD	Age (0–9 vs 10–13 vs 14–16 vs 17–24 y) Sex	Surgery (resection, stricturoplasty, stoma creation)	Mean 4.3 y
Cucchiara (2007, WJG)	Retrospective, multicenter	200 pediatric CD Mean 12 (SD 4) y, 58% M	Genetics (NOD2/CARD15 variant)	Surgery (resection)	Median 2.8 y (range 1 d-16.7 y)
De Greef (2013)	Retrospective, multicenter	155 pediatric CD Median 12.5 (range 1.6-18) y, 55% M	Gestational age, family history of IBD, disease severity at diagnosis, disease location/behavior Height and BMI z-score at diagnosis	Height and BMI z-score over F/U PCDAI, PGA, surgery (IBD-related), medication use	Median 2.7 (range 0.3-8.2) y
Desir (2004)	Combined retrospective and prospective, single center	61 pediatric CD Mean 10.7 (3.4) y, 49% M	ASCA (IgA, IgG, positivity, and titer)	B3 (fistula or abscess) Surgery (small or large bowel) Relapse	Mean 4.9 (SD 2.1) y
Dubinsky (2006)	Prospective, multicenter	167 pediatric CD Median 12 (range 1–18) y, 47% M	ASCA, OmpC, I2 and/or CBir1 Antibody sum score	B2 or B3	Median 18 (range 1–200) mo
Dubinsky (2008)	Prospective, multicenter	536 pediatric CD Median 12 (range 0.6–18) y, 56% M	ASCA, OmpC, CBir1	B2 or B3 Surgery (small or large bowel resection, perianal surgery)	Median 32 mo
Eidelwein (2007)	Retrospective, single center	137 pediatric CD, mixed cohort Mean 12.6 (SD 4.1) y, 47% M (Black) Mean 11.6 (SD 4.5) y, 52% M (White)	Race (Black vs White)	B2 or B3 Growth (weight- and height-for-age z-score) Medication use Surgery (colectomy, intestinal resection, ileostomy, fistulectomy)	Mean 5.3 (SD 3.0) y (Black) Mean 4.8 (SD 3.2) y (White) (Growth at 1 y)
Fabian (2017)	Retrospective, single center	63 pediatric CD Median 12 (range 11–15) y, 57% M	Age (continuous)	Complications (stricture that cannot be passed or with upstream dilatation, internal fistula or abscess, perianal fistula or anti-TNFα use)	1 y
Ferraris (2006)	Retrospective, multicenter	134 pediatric CD Median 12 (IQR 9.5–13) y, 51% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (abdominal surgery)	N/A
Gupta (2006)	Retrospective, multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57%	Sex, age (0–2, 3–5, 6–12, 13–17 y) Ethnicity (Caucasian, Black, Asian/Pacific	Surgery (partial SB resection, partial/total colectomy)	Mean 3.6 (SD 3.1) y

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		M	Islander, Hispanic, other) Poor growth (at presentation, not further defined) Disease location, severity (PCDAI) Granuloma, serologies		
Gupta (2008)	Retrospective (registry), multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57% M	Age (6–17 vs 0–5 y) Poor growth (at presentation, not further defined)	B2, B3 (fistula, abscess), perianal fissure Medication use Growth failure (height-for-age or height velocity <5th percentile) Compression fracture or osteopenia/osteoporosis Intensified treatment	Median 2.8 y (range 1 d – 16.7 y)
Gupta (2010)	Retrospective (registry), multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57% M	Disease location (isolated SB vs SB + colonic vs isolated colonic)	B2, B3	Median 2.8 y (range 1 d – 16.7 y) CI reported at 10 y
Henderson (2015)	Retrospective, multicenter	181 CD Median 11.6 y (9.5–13.1), 57% M	Age (0–9 vs 10–16 y) CRP at diagnosis	Surgery	Median 5.2 y
Herman (2017)	Retrospective, single center	209 pediatric CD Median 14.2 (IQR 12–16) y, 58% M	Perianal disease (fistulizing or non-fistulizing)	B2 or B3	Median 8.5 (IQR 5.2–11.7) y
Ideström (2005)	Retrospective, single center	58 pediatric CD Median 10.9 (range 2.8–16.9) y, 62% M	Genetics (NOD2/CARD15 variant)	B2 Surgery (luminal for stricture/fistula, not perianal)	Median 4.2 (range 0.9–9.7) y
Jakobsen (2014)	Case control	244 pediatric CD (mixed IBD cohort) Median 13.4 (11.6–14.0) y, 54% M	Genetics (NOD2/CARD15 variant)	Surgery	Median 4.7 y (3–7) y (entire IBD cohort)
Kugathasan (2004)	Prospective, multicenter	163 pediatric CD (138 with CARD15 data) Mean 12.4 (range 3–18) y, 58% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (ileocolonic or ileal resection)	Mean 39 (range 6–88) mo
Kugathasan (2017)	Prospective, multicenter	913 pediatric CD Median 12.3–15.6 y, 62% M	Age (continuous) Race (Black vs other) Disease location (ileal vs ileocolonic vs isolated colonic) Antimicrobial serologies Genetics (NOD2/CARD15 variant)	B2, B3	Median 40–47 mo
Lacher (2010)	Prospective, multicenter	171 pediatric CD Mean 11.8 (SD 3.2) y, 67% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (intestinal resection)	Median 4.76 (range 0.25–13.14) y
Leonor (2007)	Retrospective, single center	280 pediatric CD Median 11.9 (IQR 11.5–12.28) y, 60% M	Sex, ethnicity Disease location (small bowel disease vs ileocolon or colon)	Surgery (SB resection, subtotal/total colectomy, abscess I/D, Hartmann diversion of biopsy fistula in ano)	Median 3.27 (IQR 3.02–3.52) y
Li (2013)	Retrospective, single center	107 pediatric IBD Mean 11.2 (± 4.1) y	Race (SA vs other)	B3 (fistula) Medication use	Mean 4 (± 2.9) y Min 1 y
Malmborg (2015)	Retrospective, multicenter	161 pediatric CD 32% <10 y, 59% M	Age (>10 vs <10 y) Disease location (ileal or ileocolonic vs colonic)	B2 or B3 (or surgery)	Median 8.8 y
Na (2015)	Retrospective, single center	65 pediatric CD Mean 8.6 ± 8.6 y, 58% M	Genetics (NOD2/CARD15 variant)	B2 or B3	N/A

Posovszky (2013)	Prospective, single center	85 pediatric CD Median 22 (17–35) y group 1; 20 (15–26) y group 2, 54% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery	Min 2 y
Rieder (2012)	Prospective, single center	59 pediatric CD Mean 152 (SD 43) mo, 61% M	gASCA+	B2 or B3 (or perianal fistula) Surgery	N/A
Rinawi (2016, DLD)	Retrospective, single center	174 pediatric CD 13% <10 y, 74% 10–17 y, 13% 17–18 y	Age, sex Disease location (ileal vs other), microscopic involvement, granulomas Perianal disease (tags/fissures) Growth impairment (G1 vs G0 as per Paris classification)	B2, B3 Perianal disease Disease extension	Median 16.4 (± 4.4) y Min 10 y
Rinawi (2016, IBD)	Retrospective, single center	482 pediatric CD, 13.8 ±3 y	Sex Disease location (ileal, ileocolonic or colonic), disease behavior Growth impairment (G1 vs G0 as per Paris classification)	Surgery (intestinal surgery, stricturoplasty or fistulectomy)	Median 8.6 ± 6.6 y
Russell (2005)	Retrospective, multicenter	167 pediatric CD Median 11.5 y, 54% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (any except exam under anesthesia)	2 y
Savoye (2012)	Retrospective, multicenter	309 pediatric CD Median 14 (range 12–16) y, 54% M	Sex, age Disease location, behavior, perianal disease Diagnostic delay Growth delay, EIM	"Disabling" CD – growth delay (BMI, weight or height <–2 SDS), or 1 intestinal resection or 2 perianal interventions	Median 8 (range 7–12) y, min 5 y
Schaefer (2010)	Prospective, multicenter	498 pediatric CD 5% 0–5y, 56% 6–12 y, 39% 13–16y, 58% M	Age, sex, ethnicity Family history of IBD Disease severity, disease behavior, distal disease (between transverse colon and rectum) vs other	Surgery (intestinal resection with anastomosis or ostomy, including subtotal/total colectomy, stricturoplasty or appendectomy)	Median 2 (95% CI 1.75–2.25) y
Shaoul (2009)	Retrospective, single center	128 pediatric CD Mean 12.8 ± 3.8 y, 62% M	Age (<10, 10–12, >12 y) Genetics (NOD2/CARD15 – multiple alleles or heterozygote) Disease location Ethnicity (Sephardic vs Ashkenazi Jews)	B2, B3 Surgery	Mean 4.9 ± 3.6 y Min 2 y
Strisciuglio (2014)	Retrospective, single center	74 pediatric CD Median 11 (range 0.7–17.9) y, 66% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery Number of relapses	Min 1 y
Sun (2003)	Retrospective, single center	55 pediatric CD Mean 11.2 (range 1–17.5) y	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (intestinal resection)	N/A
Sykora (2006)	Prospective, multicenter	46 pediatric CD Mean 15.3 (SD 2.8) y, 54% M	Age (continuous) Disease location (isolated SB vs SB + colonic vs isolated colonic) Genetics (TNFα polymorphism)	B2, B3 (internal fistula, inflammatory mass/abscess, perianal fistula) Surgery (luminal resection)	N/A
Tomer (2003)	Retrospective, single center	101 pediatric CD Mean 11.8 (0.3–18) y, 66% M	Genetics (NOD2/CARD15 variant)	B2, B3	Mean 49 mo (range 28 d – 141 mo)
Vernier-Massouille (2008)	Retrospective, multicenter	404 pediatric CD Median 14 (range 12–16) y, 54% M	Sex, age Disease location (ileal or ileocolonic vs colonic), disease behavior Perianal disease	Surgery (partial SB resection, partial/total colectomy)	Median 84 (range 52–124) mo

			Growth delay (BMI ≤–2 SD)		
Zwintscher (2015)	Retrospective (health administrative database), multicenter	7845 pediatric (<20 y) CD, mixed cohort Mean 15.6 (SD 3.9) y, 51% M	Sex, age (0–5 vs 6–10 vs 11–15 vs 16–20 y) Perianal disease (fistula, abscess, fissure)	B3 (complex fistula, entero-enteral fistula) Perianal disease Growth failure (ICD-9 code) Surgery	N/A

ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CD, Crohn's disease; CI, cumulative incidence; CRP, C-reactive protein; d, days; EIM, extraintestinal manifestations; F/U, follow-up; IBD, gASCA, anti-glycan ASCA; inflammatory bowel disease; ICD, International Classification of Diseases; I/D, incision and drainage; Ig, immunoglobulin; IQR, interquartile range; LB, large bowel; M, male; mo, months; N/A, not available; pANCA, perinuclear antineutrophil cytoplasmic antibody; PCDAI, Pediatric Crohn's Disease Activity Index; PGA, Physician Global Assessment; SA, South Asian; SB, small bowel; SD, standard deviation; SDS, standard deviation scores; SEM, standard error of the mean; TNF, tumor necrosis factor; y, year

Table 2. Risk of Bias for Studies Examining Outcomes Included in Meta-Analysis

Study	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Aloi (2013)	1	1	1	0	0	1	1	1	6
Ammoury (2011)	1	1	1	1	0	1	1	1	7
Amre (2006)	1	1	1	1	2	1	1	1	9
Attard (2004)	1	1	1	1	0	1	0	1	6
Birimberg-Schwartz (2016)	1	1	1	1	1	1	1	1	8
Chhaya (2015)	1	1	1	1	2	1	1	1	9
Cucchiara (2007)	1	1	0	0	1	1	1	1	6
De Greef (2013)	1	1	1	1	0	1	1	1	7
Desir (2004)	1	1	1	1	2	1	1	1	9
Dubinsky (2006)	1	1	1	1	0	1	1	1	7
Dubinsky (2008)	1	1	1	1	0	1	1	1	7
Eidelwein (2007)	1	1	1	1	0	1	1	1	7
Fabian (2017)	1	1	1	1	2	1	0	1	8
Ferraris (2006)	1	1	1	0	0	1	0	1	5
Gupta (2006)	1	1	1	1	2	1	1	1	9
Gupta (2008)	1	1	1	0	0	1	0	1	5
Gupta (2010)	1	1	1	0	0	1	1	1	6
Henderson (2015)	1	1	1	1	2	1	1	1	9
Herman (2017)	1	1	1	1	0	1	1	1	7
Jakobsen (2014)	1	1	1	1	2	1	1	1	9
Ideström (2005)	1	1	1	0	0	1	1	1	6
Kugathasan (2004)	1	1	1	0	1	1	1	1	7
Kugathasan (2017)	1	1	1	1	2	1	1	1	9
Lacher (2010)	1	1	1	0	0	1	1	1	7
Leonor (2007)	1	1	1	1	1	1	1	0	7
Li (2013)	1	1	1	1	0	0	0	1	5
Malmborg (2015)	1	1	1	1	2	1	1	1	9
Na (2015)	1	1	1	0	0	1	0	1	5
Posovszky (2013)	1	1	1	0	0	1	1	1	6
Rieder (2012)	1	1	1	0	1	1	0	1	6
Rinawi (2016, DLD)	1	1	1	1	1	1	1	1	8
Rinawi (2016, IBD)	1	1	1	1	2	1	1	1	9
Russell (2005)	1	1	1	0	2	1	1	1	8
Savoye (2012)	1	1	1	1	1	1	1	0	7
Schaefer (2010)	1	1	1	1	2	1	1	0	8
Shaoul (2009)	1	1	1	0	0	1	1	1	6
Strisciuglio (2014)	1	1	1	0	0	1	0	1	5
Sun (2003)	1	1	1	0	0	1	0	1	5
Sykora (2006)	1	1	1	0	0	1	0	1	5
Tomer (2003)	1	1	1	0	0	1	1	1	6
Vernier-Massouille (2008)	1	1	1	1	2	1	1	1	9
Zwintscher (2015)	1	1	1	0	1	0	0	1	5

Based on Newcastle-Ottawa Scale

All columns 0 or 1 stars except comparability (0 to 2), last column = total # of stars

Table 3. Findings from Individual Studies Examining Predictor-Outcome Combinations Included in Meta-Analysis

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Growth impairment as a predictor of surgery											
Gupta (2006)	Surgery	Growth impairment (not further defined)	128/956				1.99 (1.18–3.37)	**0.01**		2.16 (1.24–3.77)	**0.007**
*De Greef (2013)	Surgery	Height- and BMI-for-age z-score at diagnosis	17/155					NS			
Rinawi (2016)	Surgery	Growth impairment (as per Paris classification)	143/482	42/107	101/375		1.6 (1.1–2.3)	**0.011**			NS
*Savoye (2012)	Surgery (composite outcome)	Growth delay BMI, weight or height <−2 SDS	47/309					**<0.05**			
*Zwintscher (2015)[2]	Surgery	Growth impairment (as per ICD-9)	2,113/ 12,465						1.21 (0.86–1.71)		0.279
Disease location as a predictor of surgery											
*Ammoury (2011)	Surgery	Esophageal involvement	9/81					0.09			
Amre (2006)	Surgery	Colon only vs other	35/139	4/32	31/107			0.07			
*Attard (2004)	Surgery	Jejunum or proximal ileum	/134	11/23	12/111	3.7		**<0.03**			
*De Greef (2013)	Surgery	Disease location	17/155					NS			
Gupta (2006)	Surgery	L2 (colonic) vs L1 (isolated ileal)	/600	/144	/456		0.56 (0.27–1.16)	0.12			
*Leonor (2007)	Surgery	Disease location	55/280					NS			
*Henderson (2015)	Surgery	Disease location	/465					NS			
Rinawi (2016, IBD)	Surgery	Colon only vs other for proportions (2x2); L2 vs L1 for HR	143/482	7/58	136/424			**0.003**		0.70 (0.51–0.96)	**0.03**
Schaefer (2010)	Surgery	Transverse colon to rectum vs other	57/854	/674	/180					0.35 (0.19–0.64)	**0.0007**
*Savoye (2012)	Surgery (composite outcome)	UGI disease	47/309					NS			
*Shaoul (2009)	Surgery	(Ileo)colonic disease	38/128					**<0.04**			
Vernier-Massouille (2008)	Surgery	L2 vs L1	176/353				0.60 (0.33-1.10)	0.1			
Sex as a predictor of surgery											
Aloi (2013)	Surgery	Male vs female	4/36	3/25	1/11			NS			
Amre (2006)	Surgery	Male vs female	35/139	15/72	20/67			NS			
Chhaya (2015)	Surgery	Male vs female	/1,595				0.90 (0.69–1.17)	0.43			
Dubinsky (2008)	Surgery	Male vs female	140/796							0.59 (0.38–0.91)	**<0.009**
Gupta (2006)	Surgery	Male vs female	128/989	63/566	65/423			NS		0.65 (0.46–0.93)	**0.02**
Leonor (2007)	Surgery	Male vs female	55/280	35/167	20/113			NS			
Rinawi (2016)	Surgery	Male vs female	143/482	86/280	57/202		1.05 (0.75–1.47)	0.78		0.98 (0.68–1.41)	0.92
Schaefer (2010)	Surgery	Male vs female	57/854	36/498	21/356			NS			
Vernier-Massouille (2008)	Surgery	Male vs female	/394				0.96 (0.71–1.30)	0.77			NS
*Zwintscher (2015)[2]	Surgery	Male vs female	2,113/						1.17 (1.06–		**0.001**

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			12,465					1.30)		
NOD2/CARD15 polymorphisms as a predictor of surgery										
Cucchiara (2007)	Surgery	NOD2/CARD15 variant	50/196	23/75	27/121		NS			
*Dubinsky (2008)	Surgery	NOD2/CARD15 variant					NS			
Ferraris (2006)	Surgery	NOD2/CARD15 variant	12/134	4/50	8/84	0.83 (0.24–2.90)	1			
*Jakobsen (2014)	Surgery	Genetic variants including NOD2/CARD15 variant	/244				NS			
Kugathasan (2004)	Surgery	NOD2/CARD15 variant	/163						7.78 (2.74–22.1)	**<0.0005**
Lacher (2010)	Surgery	NOD2/CARD15 variant	32/171	21/78	11/93	2.75 (1.23–6.14)	**0.017**			
*Posovsky (2013)	Surgery	NOD2/CARD15 variant	/85	/37	/48		NS			
Russell (2005)	Surgery	NOD2/CARD15 variant	45/167	18/33		4.45 (1.98–10.00)	**0.0002**			
*Shaoul (2009)	Surgery	NOD2/CARD15 variant	38/128	/48	/77		NS			
Strisciuglio (2014)	Surgery	NOD2/CARD 15 variant	10/74	2/16	8/58		0.89			
Sun (2003)	Surgery	NOD2/CARD15 variant	17/55	13/36	4/19		0.26			
Stricturing disease (B2) as a predictor of surgery										
De Greef (2013)	Surgery	B2	20/155			6.8 (1.8–25.3)	**0.001**			
Schaefer (2010)	Surgery	B2	57/854						6.60 (3.39–12.86)	**<0.0001**
Vernier-Massouille (2008)	Surgery	B2	176/394	/96					2.54 (1.59–4.05)	**<0.01**
Internal penetrating disease (B3) as a predictor of surgery										
Schaefer (2010)	Surgery	B3	57/854						3.70 (1.80–7.60)	**0.0005**
Vernier-Massouille (2008)	Surgery	B3	176/394	/11					1.28 (0.33–4.89)	0.72
Stricturing and/or internal penetrating disease (B2/B3) as a predictor of surgery										
Rinawi (2016)	Surgery	B2 and/or B3	143/482	51/115	92/367	2.38 (1.54–3.69)			2.44 (1.69–3.53)	**<0.001**
Antimicrobial serologies as a predictor of surgery										
Amre (2006)	Surgery	ASCA+ (IgA or IgG)	35/139	24/75	11/64		0.05		1.80 (0.84–3.85)	**<0.05**
*Birimberg-Schwartz	Surgery	pANCA-/ASCA+	6/146				0.326			
*Desir (2004)	Surgery	ASCA IgG	/154			2.34 (0.29–18.5)				
Dubinsky (2008)	Surgery	ASCA+	61/563			2.2 (1.5–3.2)	**0.0001**		3.2 (1.1–9.5)	**<0.04**
Gupta (2006)	Surgery	ASCA+	/161	7/63	/98	3.43 (1.00–11.76)	0.05			
Rieder (2012)	Surgery	gASCA+	20/59		/22				1.4 (0.4–5.0)[2]; 1.9 (0.55–6.4)[3]; 2.5 (0.64–9.4)[4]	0.59; 0.32; 0.19
Rinawi (2016)	Surgery	ASCA+	94/170	25/32	69/138	3.10 (1.34–7.19)	**0.008**			NS
Russell (2009)	Surgery	ASCA+	49/197	27/82	22/115	2.11 (1.10–4.06)	**0.03**			

Study	Type	Predictor	Total	n/N	n/N	OR (CI)	P	HR/OR (CI)	P
Age as a predictor of stricturing (B2) disease									
*Gupta (2008)	B2	Age (6–17 vs 0–5 y)	/989	/857	/83		2.15 (0.99–4.69)	0.05	
*Kugathasan (2017)	B2	Age (continuous)	54/913					1.07 (0.97–1.17)	0.16
*Shaoul (2009)	B2	Age (<10, 10–12, >12 y)	20/128				NS		
Race as a predictor of stricturing (B2) disease									
*Kugathasan (2017)	B2	Black vs other	54/913	9/121	45/792		0.45	1.08 (0.52–2.22)	0.84
Disease location as a predictor of stricturing (B2) disease									
*Aloi (2013)	B2	Disease location	/36				NS		
Gupta (2010)	B2	Ileal or ileocolonic vs colon only	/600	103/456	16/144		CI at 10 y 39.3 (14.1–80.6) (ileal) vs 18.7 (13.1–26.3) (ileocolonic) vs 11.4 (4.9–25) (colon only)	**0.02**	
Kugathasan (2017)	B2	Ileal or ileocolonic vs colon only for proportions; isolated ileal vs other for HR	54/913	44/690	10/223		0.30	1.60 (0.88–2.91)	0.12
Antimicrobial serologies as a predictor of stricturing (B2) disease									
*Aloi (2013)	B2	ASCA+ (IgA or IgG)	/36				NS		
*Kugathasan (2017)	B2	ASCA IgA+	54/913	22/218	32/695		**0.003**	1.69 (0.94–3.07)	0.0816
*Kugathasan (2017)	B2	CBir1+	54/913	32/341	22/572		**<0.001**	2.30 (1.26–4.20)	**0.007**
NOD2/CARD15 polymorphisms as a predictor of stricturing (B2) disease									
Ferraris (2006)	B2	NOD2/CARD15 variant	22/134	8/50	14/84	1.03 (0.39–2.69)	0.95		
*Ideström (2005)	B2	NOD2/CARD15 variant	7/58	/5	/53		NS		
Kugathasan (2004)	B2	NOD2/CARD15 variant	25/138	20/58	5/80		**0.0001**	7.9 (2.94–25.21)[4]	**0.0001**
*Kugathasan (2017)	B2	NOD2/CARD15 variant	54/913				0.14		
Lacher (2010)	B2	NOD2/CARD15 variant	29/171	23/78	6/93	6.06 (2.32–15.83)	**<0.0001**		
*Na (2015)	B2	NOD2/CARD15 variant					NS		
Posovszky (2013)	B2	NOD2/CARD15 variant	21/85	15/37	6/48		**0.005**		
Russell (2005)	B2	NOD2/CARD15 variant	7/167	3/33	4/134		0.14		
Shaoul (2009)	B2	NOD2/CARD15 (multiple alleles or heterozygote, any variant)	20/125	8/48	12/77		0.87		
Strisciuglio (2014)	B2	NOD2/CARD15 variant	8/74	5/16	3/58		**0.01**		
Sun (2003)	B2	NOD2/CARD15 variant	24/55	18/36	6/19	2.17 (0.67–6.96)	0.4		
Tomer (2003)	B2	NOD2/CARD15 variant	2/101	1/29	1/72		**0.5**		
Age as a predictor of internal penetrating (B3) disease									
*Gupta (2008)	B3 (fistula)	Age (6–17 vs 0–5 y)	/989	/857	/83		2.67 (1.15–6.15)	**0.02**	
*Gupta (2008)	B3 (abscess)	Age (6–17 vs 0–5 y)	/989	/857	/83		7.66 (2.36–24.9)	**0.001**	
*Kugathasan (2017)	B3	Age (continuous)	24/913					1.45 (1.17–1.80)	**0.0008**
*Shaoul (2009)	B3	Age (<10, 10–12, >12)	8/128				NS		

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Study	B3 category	Predictor	n/total					p		HR/OR	p
*Zwintscher (2015)	B3 (complex fistula)	Age (0–5 vs 6–10 vs 11–15 vs 16—20 y)	98/7,845								0.994
*Zwintscher (2015)	B3 (entero-enteral fistula)	Age (0–5 vs 6–10 vs 11–15 vs 16–20 y)	293/7,845								0.994
Race as a predictor of internal penetrating (B3) disease											
Kugathasan (2017)	B3	Black vs White	24/913	9/121	15/792			**0.001**		3.19 (1.39–7.31)	**0.0061**
Li (2013)	B3	SA vs White	15/107	3/13	12/94		CI 15.4 (4.1–4.8) vs 4.4 (1.7–11.4)	**0.02**			
Disease location as a predictor of internal penetrating (B3) disease											
*Gupta (2010)	B3	Ileal or ileocolonic vs colon only	/600	/456	/144			0.13			
*Kugathasan (2017)	B3	Ileal or ileocolonic vs colon only for proportions; isolated ileal vs other for HR	24/913	21/690	3/223			0.18		1.23 (0.51–2.95)	0.64
Antimicrobial serologies as a predictor of internal penetrating (B3) disease											
Amre (2006)	B3	ASCA IgA+	31/139	23/67	8/72			**0.002**		2.84 (1.20–6.72)	**<0.05**
*Desir (2004)	B3	ASCA IgA+	13/61						0.51 (0.08–3.08)		NS
Kugathasan (2017)	B3	ASCA IgA+	24/913	14/218	10/695			**0.0002**		2.68 (1.19–6.04)	**0.0171**
*Amre (2006)	B3	ASCA IgA titer	31/139							1.20 (1.08–1.34)	**<0.005**
*Desir (2004)	B3	ASCA IgA titer	13/61						1.04 (0.29–3.76)		NS
Amre (2006)	B3	ASCA IgG+	31/139	17/59	14/80			0.12		2.38 (1.09–5.17)	**<0.05**
Desir (2004)	B3	ASCA IgG+	13/61						0.72 (0.14–4.22)		NS
*Amre (2006)	B3	ASCA IgG titer	31/139							1.12 (0.99–1.28)	NS
*Desir (2004)	B3	ASCA IgG titer	13/61						0.91 (0.29–2.75)		NS
*Amre (2006)	B3	ASCA IgA+ or IgG+	31/139	23/75	8/64			**0.01**		2.33 (0.99–5.50)	NS
*Kugathasan (2017)	B3	CBir1+	24/913	16/341	8/572			**0.005**		3.01 (1.31–6.93)	**0.0097**
Perianal disease as a predictor of internal penetrating (B3) disease											
*Zwintscher (2015)	B3 (complex fistula)	Perianal disease (abscess, fissure, fistula)	98/7,845						3.50 (1.98–6.20)		**<0.001**
*Zwintscher (2015)	B3 (entero-enteral fistula)	Perianal disease (abscess, fissure, fistula)	293/7,845						0.30 (0.15–0.63)		**0.001**
NOD2/CARD15 polymorphisms as a predictor of internal penetrating (B3) disease											
Ferraris (2006)	B3	NOD2/CARD15 variant	14/134	7/50	7/84	1.8 (0.58–5.55)		0.3			
Kugathasan (2004)	B3	NOD2/CARD15 variant	24/138	8/58	16/80			0.34	0.64 (0.24–1.58)[4]		0.345
*Kugathasan (2017)	B3	NOD2/CARD15 variant	54/913					0.39			
Lacher (2010)	B3	NOD2/CARD15 variant	2/171	2/78	0/93			0.24			
*Na (2015)	B3	NOD2/CARD15 variant						NS			
Posovszky (2013)	B3	NOD2/CARD15 variant	21/85	6/37	3/48			0.16			
Russell (2005)	B3	NOD2/CARD15 variant	24/167	7/33	17/134			0.22			
Shaoul (2009)	B3	NOD2/CARD15 (multiple alleles or heterozygote, any variant)	8/125	5/48	3/77			0.16			

Study	Type	Predictor									
Strisciuglio (2014	B3	NOD2/CARD15 variant	4/74	4/16	0/58			**0.01**			
Sun (2003)	B3	NOD2/CARD15 variant	12/55	7/36	5/19	0.68 (0.18–2.51)		0.82			
Tomer (2003)	B3	NOD2/CARD15 variant	19/101	3/29	16/72			0.18			
Age as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
*Fabian (2017)	B2 or B3 (or perianal fistula or anti-TNF)	Age (continuous)	19/63							RR 0.95 (0.85–1.05)	0.29
*Malmborg (2015)	B2 or B3 (or anti-TNF use)	Age (>10 vs <10 y)	/161	/51	/110	1.81 (0.83–3.99)		0.14		1.00 (0.35–2.85)	0.99
*Rinawi (2016)	B2 or B3	Age (continuous)	80/174			1.02		0.47			NS
*Sykora (2006)	B2 or B3 (or perianal fistula)	Age	16/46					NS			
Race as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
*Eidelwein (2007)	B2 or B3	Race (Black vs White)	21/137	10/34	11/103			**0.01**			
Disease location as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Gupta (2010)	B2 or B3	Ileal or ileocolonic vs colon only	/600	207/456	32/144	CI at 10 y 57.7 (33.5–83.6) (ileal) vs 42.5 (32.9–53.7) (ileocolonic) vs 22.4 (14.4–33.8) (colon only)		**0.0009**			
*Malmborg (2015)	B2 or B3 (or anti-TNF use)	Ileal or ileocolonic vs colon only	/161	/130	/31	1.38 (0.63–3.03)		0.44			
Rinawi (2016)	B2 or B3	Ileal or ileocolonic vs other for proportions; isolated ileal vs other for HR	80/173	63/127	17/46	1		0.52			
Sykora (2006)	B2 or B3 (or perianal fistula)	Isolated SB or SB + colonic vs colon only	16/46	14/41	2/5			0.80			
Antimicrobial serologies as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Dubinsky (2006)	B2 or B3	Seropositive (ASCA, OmpC, I2 and/or CBir1+)	10/167	8/97	2/70			**0.03** (log-rank)			
Dubinsky (2008)	B2 or B3	Seropositive (ASCA, OmpC and/or CBir1+)	37/536	32/363	5/173			**0.01**			
*Dubinsky (2008)	B2 or B3	Antibody sum score (1–3 for each positive antibody vs 0)	37/536			1.1 (0.3–3.7) 5.5 (2.0–15.2) 6.0 (1.7–20.5)		NS **0.005** **<0.005**			
*Dubinsky (2008)	B2 or B3	ASCA+	37/536					NS			
*Dubinsky (2008)	B2 or B3	OmpC+	37/536			2.4 (1.2–4.9)		**0.01**			
*Dubinsky (2008)	B2 or B3	CBir1+	37/536			2.5 (1.2–5.2)		**<0.02**			
*Rieder (2012)	B2 or B3 (or perianal fistula)	gASCA+	/59	/37	/22					7.4 (1.4–38.2)[2] 3.9 (1.08–13.8)[3] 2.5 (0.68–9.0)[4]	**0.016** **0.038** 0.17
Perianal disease as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Herman (2017)	B2 or B3	Perianal disease (fistulizing or non-fistulizing)	29/209	18/71	11/138			**0.001**			
Rinawi (2016)	B2 or B3	Perianal disease (tags/fissures)	80/174	10/22	70/152			0.97	0.92		

*Denotes specific predictor-outcome pairs that could not be meta-analyzed due to heterogeneity or insufficient data, including lack of CD-specific data

ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CI, cumulative incidence; gASCA, anti-glycan ASCA; HR, hazard ratio; ICD, International Classification of Diseases; Ig, immunoglobulin; NS, not significant; OR, odds ratio; pANCA, perinuclear antineutrophil cytoplasmic antibody; RR, relative risk; SA, South Asian; SB, small bowel; SDS, standard deviation scores; TNF, tumor necrosis factor; UGI, upper gastrointestinal

[1] Unless otherwise stated to be RR

[2] Adjusted for disease location

[3] Adjusted for disease duration

[4] Adjusted for age

Table 4. Summary of Outcomes and Respective Predictors in Pediatric CD

Outcomes	Predictors	Possible predictors	No association
Surgery	• Growth impairment • Presence of genetic variants • ASCA (+)	• Adolescent diagnosis • Disease location	• Ethnicity • Presence of granulomas • Sex
Stricturing (B2)/Penetrating (B3) disease	• Ethnicity (B3) • Isolated small bowel disease (B2) • ASCA (+) and higher ASCA IgA titer (B3) • CBir1 (+) (B2/B3) • ≥1 microbial seropositivity (B2/B3) • *NOD2/CARD15* polymorphisms (B2)	• Older age at diagnosis (B3) • Isolated small bowel disease (B3) • Perianal disease (B2/B3)	• Older age at diagnosis (B2) • ASCA-IgA (B2) • Sex (B2/B3) • Family history of IBD (B2/B3) • Disease activity at baseline (B2/B3) • Granulomas (B2/B3) • Upper GI tract involvement (B2/B3) • EIM (B2/B3) • Diagnostic delay (B2/B3)
Perianal disease	• Ethnicity	• Older age at CD onset • Bacterial serology • Sex	• Genetics • ANCA (+) • Anthropometric parameters • Disease location • Disease behavior • EIM • Diagnostic delay • Disease activity
Linear growth impairment	• More active disease at baseline or over time • Diagnostic delay	• Male sex • Younger age at CD onset • Isolated small bowel disease • *NOD2/CARD15* polymorphisms • EIM	• Pubertal status • Family history of IBD • Ethnicity • Gestational age • Upper GI tract involvement • Oral involvement • Granulomas • Disease behavior • Perianal disease • Presenting symptoms
Bone disease	• Poor nutritional status (via height, weight, BMI)	• Higher clinical disease activity (PCDAI at baseline and over time)	• Sex • Disease location • Disease behavior • EIM • Granulomas • Perianal disease
Chronically active inflammatory disease		• ASCA positivity • Microscopic ileocolonic involvement • Disease activity • Disease behavior (B2/B3)	• Age • Sex • Ethnicity
Hospitalization		• Disease behavior (B2/B3) • Granulomas • Increased visceral adipose tissue	• Age • Small bowel involvement • *TNF* polymorphisms • *NOD2* variants
Future disease activity or severity	N/A		
Number of relapses	N/A		

ANCA, anti-neutrophil cytoplasmic antibody; ASCA, anti-*Saccharomyces cerevisiae* antibodies; B2, stricturing disease; B3, penetrating disease; BMI, body mass index; CD, Crohn's disease; EIM, extraintestinal manifestations; GI, gastrointestinal; IBD, inflammatory bowel disease; Ig, immunoglobin; N/A, not available; PCDAI, Pediatric Crohn's Disease Activity Index; TNF, tumor necrosis factor

Question 1: What are the prognostic factors of surgery?

Statement 1.1. Diagnosis in adolescence (>13 years of age), compared with younger age, may predict increased risk of bowel surgery within 5 years of diagnosis

Statement 1.2. Growth impairment at diagnosis predicts increased risk of bowel surgery

Statement 1.3. Disease location may predict surgery; isolated colonic disease is associated with fewer surgeries

Statement 1.4. Inconclusive evidence exists for sex as a predictor for surgery; presence of NOD2/CARD15 variants, stricturing and/or internal penetrating (B2/B3) phenotype, and positive anti-Saccharomyces cerevisiae antibodies (ASCA) status predict surgery; ethnicity and presence of granulomas at diagnosis do not predict surgery

Question 2: What are the prognostic risk factors of complications?

Stricturing (B2) and/or penetrating (B3) disease

Statement 2.1. Children who develop CD at an older age may be at increased risk of developing internal penetrating (B3) complications, but not stricturing (B2) disease

Statement 2.2. CD patients of Black ethnicity/race are more likely than White patients to develop penetrating (B3) disease

Statement 2.3. CD patients with small bowel disease (ie, L1 or L3 +/− L4b) have an increased risk of developing stricturing complications (B2) and may be at an increased risk of developing penetrating complications (B3)

Statement 2.4. Anti-microbial serologies predict progression to stricturing and/or internal penetrating complications:

    Statement 2.4.1. Antimicrobial serologies predict progression to stricturing (B2) and/or internal penetrating (B3) complications: ASCA positivity predicts progression to internal penetrating (B3) complications and may predict progression to stricturing (B2) complications; a higher ASCA immunoglobulin (Ig) A titer predicts progression to penetrating (B3) complications ;

    Statement 2.4.2. Antiflagellin (CBir1) positivity predicts progression to stricturing (B2) and/or internal penetrating (B3) complications; OmpC positivity may predict progression to stricturing (B2) and/or internal penetrating (B3) complications ;

    Statement 2.4.3. Seropositivity for ≥1 microbial serologies predicts progression to stricturing (B2) and/or internal penetrating (B3) disease; a higher number of positive serologies and higher titers may confer a greater risk

Statement 2.5. Polymorphisms in the NOD2/CARD15 gene predict ileal disease location and may predict stricturing (B2) disease, but location is inadequately controlled for

Statement 2.6. The presence of perianal disease may predict stricturing (B2) and/or internal penetrating (B3) complications

Statement 2.7. Sex, family history of IBD, disease activity at baseline, granulomas, upper GI tract involvement, presence of extraintestinal manifestations, and diagnostic delay do not predict disease location, stricturing (B2) and/or internal penetrating (B3) complications

Perianal disease

Statement 2.8. Older age at CD onset may be associated with an increased risk of developing perianal disease

Statement 2.9. Children and adolescents of Black and South Asian ethnicity with CD are at a greater risk of developing perianal disease

Statement 2.10. Bacterial serology and sex may be associated with the development of perianal disease; genetics, antineutrophil cytoplasmic antibody (ANCA) positivity, anthropometric parameters, disease location, disease behavior, extraintestinal manifestations, diagnostic delay, and disease activity do not predict the development of perianal disease

Linear growth impairment

Statement 2.11. Male sex, younger age at disease onset, and isolated small bowel disease may be associated with a greater risk of linear growth impairment

Statement 2.12. More active disease (assessed at baseline or over time) predicts linear growth impairment

Statement 2.13. Diagnostic delay is a risk factor for linear growth impairment

Statement 2.14. *NOD2/CARD15* polymorphisms may be associated with low weight, and extraintestinal manifestations may be associated with linear growth impairment; pubertal status at disease onset, family history of IBD, ethnicity, gestational age, upper GI tract involvement, oral involvement, granulomas, disease behavior, perianal disease, and presenting symptoms do not predict linear growth impairment

Bone disease

Statement 2.15. Low height, weight, and body mass index predict reduced BMD

Statement 2.16. Higher clinical disease activity (assessed by Pediatric CD Activity Index [PCDAI]) at baseline and over time may predict reduced BMD

Statement 2.17. Sex, disease location, disease behavior, extraintestinal manifestations, granulomas, and perianal disease do not predict BMD

Question 3: What are the prognostic risk factors of chronically active inflammatory disease?

Chronically active inflammatory disease

Statement 3.1. ASCA positivity may predict the need for more intensive therapy

Statement 3.2. Microscopic ileocolonic involvement at diagnosis may be associated with subsequent macroscopic ileocolonic disease

Statement 3.3. Disease activity and disease behavior (ie, B2 and/or B3), but not age and sex, may predict more intensive therapies or a poor response to therapies; there is no strong evidence for a predictive value of ethnicity

Statement 3.4. No strong evidence exists to identify predictive factors of future disease activity or disease severity

Statement 3.5. No strong evidence exists for predictors of disease relapse and the number of relapses

Statement 3.6. Stricturing and/or internal penetrating (B2/B3) phenotype and the presence of granulomas and increased visceral adipose tissue may predict hospitalizations; small bowel involvement, TNF polymorphisms, NOD2 variants, and age do not predict hospitalization

A

Study	TE	seTE	Hazard Ratio	HR	95%-CI	Weight (fixed)	Weight (random)
Gupta (ROB = 8)	0.69	0.2677		1.99	[1.18; 3.36]	33.1%	33.1%
Rinawi (ROB = 9)	0.47	0.1882		1.60	[1.11; 2.31]	66.9%	66.9%
Fixed effect model				**1.72**	**[1.27; 2.33]**	**100.0%**	--
Random effects model				**1.72**	**[1.27; 2.33]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .51$
0.5 1 2

B

Study	TE	seTE	Hazard Ratio	HR	95%-CI	Weight (fixed)	Weight (random)
Vernier-Massouille (ROB = 9)	-0.51	0.3071		0.60	[0.33; 1.10]	15.9%	19.7%
Gupta (ROB = 8)	-0.58	0.3719		0.56	[0.27; 1.16]	10.8%	14.4%
Rinawi (2016)	-0.36	0.1614		0.70	[0.51; 0.96]	57.6%	46.5%
Schaefer (2010)	-1.05	0.3098		0.35	[0.19; 0.64]	15.6%	19.4%
Fixed effect model				**0.60**	**[0.47; 0.76]**	**100.0%**	--
Random effects model				**0.57**	**[0.43; 0.78]**	--	**100.0%**

Heterogeneity: $I^2 = 24\%$, $\tau^2 = 0.0241$, $P = .26$
0.2 0.5 1 2 5

C

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Aloi (ROB = 6)	0.21	1.2257		1.23	[0.11; 13.59]	0.8%	1.1%
Amre (ROB = 8)	-0.48	0.3905		0.62	[0.29; 1.33]	8.0%	10.0%
Gupta (ROB = 8)	-0.37	0.1898		0.69	[0.48; 1.00]	33.9%	29.9%
Leonor (ROB = 7)	0.21	0.3113		1.23	[0.67; 2.27]	12.6%	14.6%
Schaefer (ROB = 8)	0.22	0.2838		1.24	[0.71; 2.17]	15.1%	16.9%
Rinawi (2016)	0.12	0.2030		1.13	[0.76; 1.68]	29.6%	27.4%
Fixed effect model				**0.93**	**[0.75; 1.16]**	**100.0%**	--
Random effects model				**0.95**	**[0.73; 1.22]**	--	**100.0%**

Heterogeneity: $I^2 = 22\%$, $\tau^2 = 0.0222$, $P = .27$
0.1 0.5 1 2 10

D

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Russel (ROB = 8)	1.49	0.4131		4.45	[1.98; 10.00]	21.7%	21.3%
Cucchiara (ROB = 5)	0.43	0.3322		1.54	[0.80; 2.95]	33.6%	26.6%
Sun (ROB = 6)	0.75	0.6611		2.12	[0.58; 7.74]	8.5%	11.3%
Ferraris (ROB = 4)	-0.19	0.6402		0.83	[0.24; 2.90]	9.0%	11.9%
Lacher (2010)	1.01	0.4102		2.75	[1.23; 6.14]	22.0%	21.4%
Strisciuglio (2014)	-0.11	0.8464		0.89	[0.17; 4.69]	5.2%	7.6%
Fixed effect model				**2.08**	**[1.43; 3.03]**	**100.0%**	--
Random effects model				**2.02**	**[1.23; 3.32]**	--	**100.0%**

Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.1316$, $P = .17$
0.1 0.5 1 2 10

E

Study	TE	seTE	Hazard Ratio	HR	95%-CI	Weight (fixed)	Weight (random)
Schaeffer (ROB = 8)	1.31	0.3674		3.70	[1.80; 7.60]	77.8%	65.0%
Vernier-Massouille (ROB = 9)	0.25	0.6877		1.28	[0.33; 4.93]	22.2%	35.0%
Fixed effect model				**2.92**	**[1.55; 5.52]**	**100.0%**	--
Random effects model				**2.55**	**[0.95; 6.88]**	--	**100.0%**

Heterogeneity: $I^2 = 46\%$, $\tau^2 = 0.2594$, $P = .17$
0.2 0.5 1 2 5

F

Study	TE	seTE	Hazard Ratio	HR	95%-CI	Weight (fixed)	Weight (random)
Schaeffer (ROB = 8)	1.89	0.3401		6.60	[3.39; 12.85]	33.0%	46.8%
Vernier-Massouille (ROB = 9)	0.93	0.2385		2.54	[1.59; 4.05]	67.0%	53.2%
Fixed effect model				**3.48**	**[2.37; 5.10]**	**100.0%**	--
Random effects model				**3.97**	**[1.56; 10.10]**	--	**100.0%**

Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.3696$, $P = .02$
0.1 0.5 1 10

G

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Dubinsky (ROB = 8)	0.79	0.1933		2.20	[1.51; 3.21]	55.2%	55.2%
Rieder (2012)	0.92	0.6855		2.50	[0.65; 9.58]	4.4%	4.4%
Russel (ROB = 8)	0.75	0.3331		2.11	[1.10; 4.05]	18.6%	18.6%
Amre (ROB = 8)	0.82	0.4136		2.27	[1.01; 5.10]	12.1%	12.1%
Rinawi (ROB = 9)	1.27	0.4603		3.57	[1.45; 8.80]	9.7%	9.7%
Fixed effect model				**2.31**	**[1.74; 3.06]**	**100.0%**	--
Random effects model				**2.31**	**[1.74; 3.06]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .90$
0.2 0.5 1 2 5

A

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Kugathasan (ROB = 9)	1.43	0.4336		4.16	[1.78; 9.74]	73.8%	73.8%
Li (ROB = 5)	0.72	0.7272		2.05	[0.49; 8.53]	26.2%	26.2%
Fixed effect model				**3.46**	**[1.67; 7.17]**	**100.0%**	--
Random effects model				**3.46**	**[1.67; 7.17]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .40$

0.2 0.5 1 2

B

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Gupta (ROB = 5)	0.85	0.2878		2.33	[1.33; 4.10]	60.9%	60.2%
Kugathasan (ROB = 9)	0.37	0.3591		1.45	[0.72; 2.93]	39.1%	39.8%
Fixed effect model				**1.94**	**[1.25; 3.01]**	**100.0%**	--
Random effects model				**1.93**	**[1.22; 3.05]**	--	**100.0%**

Heterogeneity: $I^2 = 6\%$, $\tau^2 = 0.0072$, $P = .30$

0.5 1 2

C

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Gupta (ROB = 5)	1.07	0.2214		2.91	[1.89; 4.49]	69.2%	56.5%
Rinawi (ROB = 9)	0.52	0.3533		1.68	[0.84; 3.36]	27.2%	36.1%
Sykora (ROB = 7)	-0.25	0.9705		0.78	[0.12; 5.21]	3.6%	7.4%
Fixed effect model				**2.39**	**[1.67; 3.43]**	**100.0%**	--
Random effects model				**2.16**	**[1.26; 3.71]**	--	**100.0%**

Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0857$, $P = .21$

0.2 0.5 1 2 5

D

Study	TE	seTE	Hazard Ratio	HR	95%-CI	Weight (fixed)	Weight (random)
Kugathasan (ROB = 9)	0.99	0.4144		2.68	[1.19; 6.04]	52.9%	52.9%
Amre (ROB = 8)	1.04	0.4395		2.84	[1.20; 6.72]	47.1%	47.1%
Fixed effect model				**2.75**	**[1.53; 4.97]**	**100.0%**	--
Random effects model				**2.75**	**[1.53; 4.97]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .92$

0.2 0.5 1 2 5

E

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Desir (ROB = 8)	-0.33	0.8689		0.72	[0.13; 3.95]	18.3%	19.2%
Amre (ROB = 8)	0.65	0.4114		1.91	[0.85; 4.27]	81.7%	80.8%
Fixed effect model				**1.60**	**[0.77; 3.31]**	**100.0%**	--
Random effects model				**1.58**	**[0.75; 3.36]**	--	**100.0%**

Heterogeneity: $I^2 = 3\%$, $\tau^2 = 0.0129$, $P = .31$

0.2 0.5 1 2 5

F

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Dubinsky(2006) (ROB = 7)	1.12	0.8068		3.06	[0.63; 14.86]	27.0%	27.0%
Dubinsky(2008) (ROB = 8)	1.18	0.4901		3.25	[1.24; 8.49]	73.0%	73.0%
Fixed effect model				**3.20**	**[1.41; 7.26]**	**100.0%**	--
Random effects model				**3.20**	**[1.41; 7.26]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .95$

0.1 0.5 1 2 10

G

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Shaoul (ROB = 5)	0.08	0.4987		1.08	[0.41; 2.88]	15.7%	13.6%
Strisciuglio (ROB = 8)	2.12	0.8015		8.33	[1.73; 40.09]	6.1%	8.7%
Tomer (ROB = 5)	0.93	1.4317		2.54	[0.15; 41.95]	1.9%	3.8%
Lacher (ROB = 6)	1.80	0.4897		6.06	[2.32; 15.83]	16.2%	13.8%
Posovsky (ROB = 8)	1.56	0.5501		4.77	[1.62; 14.03]	12.9%	12.7%
Russell (ROB = 8)	1.18	0.7902		3.25	[0.69; 15.29]	6.2%	8.8%
Ferraris (ROB = 4)	-0.05	0.4843		0.95	[0.37; 2.46]	16.6%	13.9%
Sun (ROB = 6)	0.77	0.5956		2.17	[0.67; 6.96]	11.0%	11.8%
Kugathasan (ROB = 9)	2.07	0.5382		7.89	[2.75; 22.67]	13.4%	12.9%
Fixed effect model				**2.95**	**[2.00; 4.34]**	**100.0%**	--
Random effects model				**3.10**	**[1.70; 5.65]**	--	**100.0%**

Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.4373$, $P = .02$

0.1 0.5 1 2

H

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Shaoul (ROB = 5)	1.05	0.7551		2.87	[0.65; 12.60]	8.6%	10.7%
Strisciuglio (ROB = 8)	3.74	1.5229		42.12	[2.13; 833.31]	2.1%	3.9%
Tomer (ROB = 5)	-0.91	0.6724		0.40	[0.11; 1.51]	10.8%	12.1%
Lacher (ROB = 6)	1.81	1.5568		6.11	[0.29; 129.21]	2.0%	3.8%
Posovsky (ROB = 8)	1.07	0.7446		2.90	[0.67; 12.49]	8.8%	10.9%
Russel (ROB = 8)	0.62	0.4987		1.85	[0.70; 4.92]	19.7%	15.8%
Ferraris (ROB = 4)	0.58	0.5674		1.79	[0.59; 5.45]	15.2%	14.2%
Sun (ROB = 6)	-0.39	0.6699		0.68	[0.18; 2.51]	10.9%	12.2%
Kugathasan (ROB = 9)	-0.45	0.4724		0.64	[0.25; 1.62]	21.9%	16.4%
Fixed effect model				**1.31**	**[0.85; 2.02]**	**100.0%**	--
Random effects model				**1.48**	**[0.78; 2.81]**	--	**100.0%**

Heterogeneity: $I^2 = 48\%$, $\tau^2 = 0.4320$, $P = .05$

0.01 0.1 1 10 100

I

Study	TE	seTE	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
Herman (ROB = 7)	1.37	0.4162		3.92	[1.73; 8.86]	54.8%	50.9%
Rinawi (ROB = 9)	-0.02	0.4581		0.98	[0.40; 2.40]	45.2%	49.1%
Fixed effect model				**2.09**	**[1.14; 3.82]**	**100.0%**	--
Random effects model				**1.98**	**[0.51; 7.74]**	--	**100.0%**

Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.7752$, $P = .02$

0.2 0.5 1 2 5

Supplemental Materials for Crohn's Disease (CD)

Supplemental Methods

Search string for Cochrane

('crohn*' or 'ulcerative colitis' or 'inflammatory bowel diseas*' or 'IBD') and ((infant or pediatric or paediatric or adolescent or teenagers or teens) and (predict* or prognos* or surgery or colectomy or resection or 'steroid depend*' or hospitalization* or complication or stenosis or fistul* or 'penetrat*' or growth or height or osteopenia or osteoporosis or 'acute severe colitis' or cancer or malignancy or lymphoma or 'colorectal carcinoma' or 'colorectal cancer' or 'colon cancer' or adenocarcinoma or death or mortality or outcome or 'quality of life' or melanoma))

Search string for Embase

'crohn*' OR 'ulcerative colitis' OR 'inflammatory bowel diseas*' OR 'ibd' AND (infant OR pediatric OR paediatric OR adolescent OR teenagers OR teens) AND (predict* OR prognos* OR surgery OR colectomy OR resection OR 'steroid depend*' OR hospitalization* OR complication OR stenosis OR fistul* OR 'penetrat*' OR growth OR height OR osteopenia OR osteoporosis OR 'acute severe colitis' OR cancer OR malignancy OR lymphoma OR 'colorectal carcinoma' OR 'colorectal cancer' OR 'colon cancer' OR adenocarcinoma OR death OR mortality OR outcome OR 'quality of life' OR melanoma) AND [english]/lim AND [1992-2017]/py

Search string for PUBMED

("crohn$"[Mesh Terms] OR "crohn$"[all fields])

OR ("ulcerative colitis"[Mesh Terms] OR "ulcerative colitis"[all fields] OR UC[Mesh Terms] OR

UC[all fields]) OR ("inflammatory bowel diseas$"[Mesh Terms] OR "inflammatory bowel

diseas$"[all fields] OR "IBD"[Mesh Terms] OR "IBD"[all fields]))

AND ((infant[mesh] OR pediatric[mesh] OR paediatric[mesh] OR adolescent[mesh] OR

teenagers[mesh] OR teens[mesh]) AND (predict$[all fields] OR prognos$[all fields] OR

surgery[all fields] OR colectomy[all fields] OR resection[all fields] OR "steroid depend$"[all

fields] OR hospitalization$[all fields] OR complication[all fields] OR stenosis[all fields] OR

fistul$[all fields] OR penetrat$[all field] OR growth[all fields] OR height[all fields] OR

osteopenia[all fields] OR osteoporosis[all fields] OR "acute severe colitis"[all fields] OR

cancer[all fields] OR malignancy[all fields] OR lymphoma[all fields] OR "colorectal

carcinoma"[all fields] OR "colorectal cancer"[all fields] OR "colon cancer"[all fields] OR

adenocarcinoma[all fields] OR death[all fields] OR mortality[all fields] OR outcome[all fields] OR

"quality of life"[all fields] OR melanoma[all fields]))) AND english[la] AND

"1992/01/01"[pdat]:"2017/06/01"[pdat]

Supplemental Results

Prognostic Factors for Surgery

Statement 1.1. Diagnosis in adolescence (>13 years of age), compared with younger age, may

predict increased risk of bowel surgery within 5 years of diagnosis (94% agreement).

Age at diagnosis was examined as a risk factor for surgery in multiple studies, with

conflicting outcomes. In a registry study (the Pediatric IBD Consortium Registry), risk of surgery

significantly increased with age among 989 children with CD diagnosed between 0 and 17 years

(adjusted hazard ratio [aHR] 1.12 per 1-year increase in age, 95% confidence interval [CI] 1.06–1.18, *P*<.0001). The children were divided into four age groups (0–2, 3 –5, 6–12, and 13–17 years), with risk for surgery significantly higher among children diagnosed at a younger age than among those diagnosed at 13–17 years (age of diagnosis 3–5 years: hazard ratio [HR] 0.20, 95% CI 0.07–0.57, *P*=.003; age of diagnosis 6–12 years: HR 0.53, 95% CI 0.36–0.77, *P*=.0008).[1] In contrast, data from 854 children with CD from the Pediatric Inflammatory Bowel Disease Collaborative Research Group indicated that older age at diagnosis was significantly associated with increased risk of bowel surgery, including intestinal resection, strictureplasty, or appendectomy (HR 1.1, 95% CI 1.01–1.03, *P*=.042).[2] Similarly, a 5-year follow-up study of children with IBD (19 with CD) found that children who had surgery owing to stricturing disease (mean age 11.0 years, 95% CI 8.0–14.0) were significantly younger at diagnosis than children who had not received surgery (mean age 14.2 years, 95% CI 13.3–15.1, *P*=.03).[3]

Age was not significantly associated with risk for surgery across seven studies. In a study of 506 children with IBD, risk for surgery was equal across three groups (0–5 years, 6–11 years, and 12–18 years).[4] A United Kingdom retrospective study of patients with IBD (1,595 with CD) reported no significant difference in risk for surgery between those diagnosed at 14–16 years and those diagnosed at 17–24 years (HR 1.34, 95% CI 0.95–1.89, *P*=.09).[5] In a natural history study of 404 children with CD, the risk for surgery was not significantly different among children diagnosed at <10 years at diagnosis (HR 0.66, 95% CI 0.36–1.21, *P*=.18).[6] Four studies with smaller numbers of CD patients who underwent surgery also found age not to be a significant predictor.[7-10]

Statement 1.2. Growth impairment at diagnosis predicts increased risk of bowel surgery (81% agreement).

Growth impairment, as assessed by weight, height, and body mass index (BMI), was consistently identified as a risk factor for surgery in multiple studies.

In the natural history study of CD described earlier, growth delay (BMI ≤2 standard deviations [SD]) was associated with an increased risk of first resection surgery (HR 1.68, 95% CI 1.16–2.44, *P*=.01).[6] A chart review of 482 children with CD reported a significantly increased risk for children with growth impairment at diagnosis (HR 1.6, 95% CI 1.1–2.3, *P*=.011), particularly for lower weight *z*-score at diagnosis (HR 0.86, 95% CI 0.75–0.99, *P*=.035).[11] In the Pediatric IBD Consortium Registry study, poor growth (based on clinicians' observations) was the only symptom at disease onset that was significantly associated with risk for surgery (HR 1.99, 95% CI 1.18–3.37, *P*=.01). This association remained significant when multivariate Cox modeling was applied (HR 2.16, 95% CI 0.26–0.94, *P*=.007).[1]

Of note, an analysis of 12,465 inpatient admissions for patients aged ≤20 years with IBD in 2009 (Kids' Inpatient Database) found that growth failure or overall developmental delay (defined as lack of development, failure to thrive, delayed milestones, or short stature) did not affect the likelihood of surgical intervention,[10] and a Belgium registry study of 255 children with CD found that height and BMI were not significantly related to the need for surgery.[9]

Statement 1.3. Disease location may predict surgery; isolated colonic disease is associated with fewer surgeries (84% agreement).

Distal disease was found to be protective in 854 children with CD from the Pediatric Inflammatory Bowel Disease Collaborative Research Group who were diagnosed with CD between 2002 and 2008. The presence of disease between the transverse colon and rectum was significantly associated with a decreased risk of surgery (P<.015), and in the subgroup of 790 patients with disease in the ileum and/or right colon, additional disease involvement between the transverse colon and rectum was associated with a decreased risk of bowel surgery (P<.004). In addition, distal disease was significantly associated with a decreased risk for surgery (HR 0.4, 95% CI 0.2–0.6, P=.007), whereas increased risks for surgery were associated with stricturing disease (HR 6.6, 95% CI 3.4–12.9, P<.0001), penetrating disease (HR 3.7, 95% CI 1.8–7.6, P=.0005), and disease severity (defined as an increase in physician global assessment [PGA], HR 2.6, 95% CI 2.0–3.5, P<.0001).[2] Furthermore, in 224 CD patients diagnosed at <20 years (mean follow-up 12.2 years), patients with only localized colonic disease were less likely to require intestinal resection (P<.05).[12]

Statement 1.4. **Inconclusive evidence exists for sex as a predictor for surgery; presence of *NOD2/CARD15* variants, stricturing and/or internal penetrating (B2/B3) phenotype, and positive anti-*Saccharomyces cerevisiae* antibodies (ASCA) status predict surgery; ethnicity and presence of granulomas at diagnosis do not predict surgery** (90% agreement).

Results were inconsistent regarding the role of sex as a predictor for surgery. An analysis of 2,113 surgeries performed across 12,465 patients from the Kid's Inpatient Database reported a lower risk for surgery in girls.[10] In contrast, girls were found to be at a significantly increased

risk for surgery in a separate analysis of the Pediatric IBD Consortium Registry data (n=989).[1]

Sex was not found to be a significant predictor for surgery in five additional studies.[5-7, 11, 13]

Evidence for *NOD2/CARD15* gene variants as a predictor of risk for surgery was mixed

across studies. A study of 186 patients found that a 3020insC mutation conferred a higher risk

for surgery.[14] A study of 32 patients undergoing surgery identified a need for significantly

earlier surgery in 15 patients with a p.1007fs mutation.[15] In a retrospective study, a higher

proportion of patients who underwent intestinal surgery than those who did not had one or

more single nucleotide polymorphisms (SNPs) in *NOD2/CARD15*.[16] A large genotypic association

study in a mixed population of adults and children, which included 2,568 CD patients of age <17

years, found that, though there was a strong association between *NOD2* and surgery, this was

no longer the case after controlled for disease location.[17] Additional pediatric studies also

observed no association between gene variants and risk for surgery.[18-24]

Complicated disease increases the risk for surgery. Stricturing disease, enteroenteral fistulas,

and complex fistulas (rectourethral, rectovaginal, or enterovesical) significantly increased the

risk for surgery.[6, 10, 11]

Circulating microbial antibodies were identified as potential predictors for surgery. In five

studies the association between a positive ASCA status and surgery was significant or bordered

the null.[1, 11, 13, 25, 26] In a retrospective chart review of children with CD from the Schneider

Pediatric Inflammatory Bowel Disease cohort identified between 1996 and 1998, a positive

ASCA status or ASCA+/perinuclear antineutrophil cytoplasmic antibody (pANCA)(−) profile was

significantly associated with an increased risk for surgery.[11] In a study of a panel of circulating

microbial antibodies, only antilaminaribioside carbohydrate antibodies (ALCA) was positively

associated with CD-related surgery after controlling for age.[27] Other small studies did not find any association between ASCA or pANCA and surgery.[28, 29]

Ethnicity was consistently not associated with risk for surgery.[1, 2, 30, 31]

The presence of granulomas was not a predictor for surgery in any of the five studies in children with CD.[1, 11, 32-34]

Prognostic Risk Factors for Complications in Pediatric CD

Statement 2.1. Children who develop CD at an older age may be at increased risk of developing internal penetrating (B3) complications, but not stricturing (B2) disease (94% agreement).

Age at diagnosis was a risk factor for progression to complicated CD, particularly internally penetrating complications. In 989 children with CD from the American Pediatric IBD Consortium Registry, children aged 6–17 years were at higher risk of developing fistulas (HR 2.67, 95% CI 1.15–6.15) and abscesses (HR 7.66, 95% CI 2.36–24.9) than children aged <5 years. Of note, the study did not stratify risk by disease location, and therefore the frequency of isolated colonic involvement, which is higher in younger children, was not controlled for.[35] In the RISK study (a large, North American, prospective inception cohort study of 913 children with CD without complicated disease at presentation), which controlled for disease location, the average age at diagnosis was older in children with CD who progressed to penetrating disease (aHR 1.45, 95% CI 1.17–1.80).[36] However, other smaller studies did not describe any association between age at diagnosis and penetrating disease[10, 24] and did not find that age at diagnosis independently predicts,[24, 36] or is significantly associated with, progression to stricturing disease, although the

mean age at diagnosis was older in those who progressed to stricturing disease (HR 2.15, 95% CI 0.99–4.69).[35]

Four studies examined age as a predictor of progression to the combined outcome of B2 or B3 complications; none found age to be significant.[37-40]

Additional evidence published since the consensus meeting was consistent with previous studies. In a Swiss IBD study comparing the risk of complications among adults and children with CD, the overall prevalence of strictures, as well as ileal and colonic stricture rates and abdominal penetrating disease, were comparable across all age groups; however, rectal, anal, duodenojejunal, and multiple strictures were more common in the youngest patients.[41] The same study found no association between age and long-term disease behavior or complications among patients <15 years treated with systemic steroids and immunomodulators.[42]

Statement 2.2. CD patients of Black ethnicity/race are more likely than White patients to develop penetrating (B3) disease (82% agreement).

In the RISK study, African American children were at higher risk of developing penetrating disease (aHR 3.19, 95% CI 1.39–7.31).[36] Similar results were reported by Eidelwein et al., where a higher proportion of Black children progressed to stricturing or penetrating disease than White children (29% of Black children vs 11% of White children, P=.05).[30] A significantly greater cumulative incidence of fistula development at 1 year was found in South Asian children (15.4%, 95% CI 4.1–48.8%) than in White children (4.4%, 95% CI 1.7–11.4%, P=.02).[43]

Statement 2.3. CD patients with small bowel disease (ie, L1 or L3 +/− L4b) have an increased risk of developing stricturing complications (B2) and may be at an increased risk of developing penetrating complications (B3) (85% agreement).

Evidence for disease location as a predictor for stricturing and/or penetrating disease is not consistent. In a retrospective cohort study of 989 children with CD by Gupta et al., isolated small bowel disease was associated with higher risk for developing stricturing complications (incidence rate 39% in children with isolated small bowel disease; 19% in children with combined small bowel and colonic involvement; 11% in children with isolated colonic disease), faster progression to complicated disease (log-rank *P*=.02) in a univariate analysis, and combined outcome of B2/B3 complications (incidence rate 58% in children with isolated small bowel disease; 43% in children with combined small bowel and colonic involvement; 22% in children with isolated colonic disease; log-rank *P*=.009 in a univariate analysis).[44] In contrast, ileal location of disease was not a risk factor for stricturing disease in the RISK study (aHR 1.60, 95% CI 0.88–2.91).[36] In an additional study of 36 children with stricturing CD, disease location was not linked to stricture formation.[7]

No association between penetrating disease and disease location was identified in the RISK study (isolated ileal disease aHR 1.23, 95% CI 0.51–2.95) or the retrospective study by Gupta et al. Three studies did not establish a link between disease location and the combined outcome of B2/B3 complications.[38-40]

Statement 2.4.1. Antimicrobial serologies predict progression to stricturing (B2) and/or internal penetrating (B3) complications: ASCA positivity predicts progression to internal

penetrating (B3) complications and may predict progression to stricturing (B2) complications; a higher ASCA immunoglobulin (Ig) A titer predicts progression to penetrating (B3) complications (94% agreement).

Antimicrobial serologies as predictors for disease complications have been examined in multiple studies.[13, 25, 29, 36, 45] ASCA status was not significantly associated with progression to stricturing disease (aHR 2.30, 95% CI 1.26–4.20) in the RISK study[36]; however, both ASCA IgA (aHR 2.68, 95% CI 1.19–6.04) and ASCA IgG (aHR 2.38, 95% CI 1.09–1.28) status were independently associated with progression to penetrating disease. Moreover, ASCA IgA and IgG positivity were associated with more rapid progression to B3 complications than negative ASCA IgA or IgG (68 vs 2074 days for ASCA IgA, and 58 vs 1225 days for ASCA IgG). The combination of ASCA positivity and antineutrophil cytoplasmic antibody (ANCA) negativity was also significantly associated with B3 disease (aHR 1.86, 95% CI 1.25–6.52).[36] Consistent with these results, ASCA IgA positivity was independently associated with progression to penetrating disease when disease location, age, and medication use were controlled (aHR 2.84, 95% CI 1.20–6.72), and a higher titer of ASCA IgA was associated with a higher risk for penetrating disease (12-unit titer increase associated with a 20% increase in hazards).[13] However, in a single-center longitudinal study of 61 children, neither ASCA IgA nor IgG was associated with progression to penetrating disease.[29]

Statement 2.4.2. Antiflagellin (CBir1) positivity predicts progression to stricturing (B2) and/or internal penetrating (B3) complications; OmpC positivity may predict progression to stricturing (B2) and/or internal penetrating (B3) complications (94% agreement).

CBir1 positivity was independently associated with penetrating complications (aHR 3.01, 95% CI 1.31–6.93) and was a predictor for B2 outcomes (aHR 2.30, 95% CI 1.26–4.20) in the RISK study.[36] In a follow-up longitudinal study of 536 children, CBir1 was significantly associated with combined B2/B3 outcomes (aHR 2.5, 95% CI 1.2–5.2, *P*<.02), although the pilot study did not describe any association.[25, 45]

Statement 2.4.3. Seropositivity for ≥1 microbial serologies predicts progression to stricturing (B2) and/or internal penetrating (B3) disease; a higher number of positive serologies and higher titers may confer a greater risk (94% agreement).

In the same longitudinal study including 536 children described above, a greater proportion of children positive for ≥1 microbial biomarker progressed to B2/B3 complication than those who were negative for all serologies (9% of children positive for ≥1 of ASCA, anti-OmpC, or anti-CBir1 developed B2 or B3 complications compared with 2.9% of children who were negative for all serologies [*P*=.01]). Additionally, a dose-dependent increase in risk for B2/B3 complications was observed, as aHRs progressively increased with rising antibody sum scores (aHR 6 for antibody sum score 3 vs 0) and increasing quartile sum scores (aHR 10 for quartile sum score group 4 vs 2).[25]

Statement 2.5. Polymorphisms in the *NOD2/CARD15* gene predict ileal disease location and may predict stricturing (B2) disease, but location is inadequately controlled for (90% agreement).

Associations between *NOD2/CARD15* and penetrating[18, 20, 21, 24, 36, 46] and stricturing complications[14-16, 18-21, 24, 36, 46-48] were examined with inconsistent results.

NOD2/CARD15 polymorphisms have been described as risk factors for stricturing disease, and despite inconsistent results across studies, a significant association was noted in the meta-analysis (*P*=.0002). In a study of 186 children, the odds of developing stricturing complications in children carrying at least one 3020insC allele were 6.6-fold higher (odds ratio [OR] 6.62, 95% CI 2.69–16.84) than children not carrying this variant.[14] Similarly, in a study of 171 children, the *NOD2* genotype and p.1007fs carrier status showed highly significant associations with stricturing complications, the odds of developing strictures were 9.8 times higher in children carrying at least one allele for p.1007fs (95% CI 4.05–23.85).[15] However, multiple studies, including the RISK study, did not observe any association between *NOD2* genotype and stricturing disease.[18-20, 24, 36, 46, 47, 49]

No association between *NOD2/CARD15* and the combined outcome of B2/B3 disease was found in two studies.[48, 50] Of note, it is difficult to estimate accurately the relationship between *NOD2* and B2/B3 complications, as it is confounded by the association between *NOD2* and ileal disease location.

Similarly, *NOD2* genotype was not associated with penetrating disease in multiple studies.[18, 20, 21, 24, 36, 46]

Statement 2.6. The presence of perianal disease may predict stricturing (B2) and/or internal penetrating (B3) complications (89% agreement).

Evidence for perianal disease as a risk factor for progression to complicated disease was examined in two studies with inconsistent results.[10, 39] A multivariate analysis demonstrated an increased risk of complex fistulas (OR 3.50, 95% CI 1.98–6.20) and decreased risk of entero-enteral fistulas (OR 0.30, 95% CI 0.15–0.63) in patients with perianal disease in 12,465 in-patients <20 years of age with IBD from the Kid's Inpatient Database in 2009.[10] However, in a study of 215 children with CD with ≥10 years of follow-up, no association between perianal disease at diagnosis and progression was identified.[39]

Statement 2.7. Sex, family history of IBD, disease activity at baseline, granulomas, upper GI tract involvement, presence of extraintestinal manifestations, and diagnostic delay do not predict disease location, stricturing (B2) and/or internal penetrating (B3) complications (83% agreement).

Sex as a predictor for progression to stricturing or penetrating diseases was examined in multiple studies, with most studies not finding any association.[7, 12, 37-40, 51]

Of note, a retrospective study of 989 children with CD reported that girls were at lower risk for developing a fistula than boys (OR 0.71, 95% CI 0.47–1.05, P=.09); furthermore, no significant difference in the risk for developing abscesses (P=.87) or strictures (P=.55) was found.[51] In contrast, in a population-based study of young patients with IBD, females were at increased risk for developing complex fistula (rectourethral, rectovaginal, or enterovesical) but at decreased risk of developing enteroenteral fistulas.[10]

A family history of IBD was not a predictor of complicated disease in multiple studies, including one registry study of 200 patients with childhood-onset CD, a longitudinal study of

215 patients with childhood-onset CD with ≥10 years of follow-up, and a study of 36 children with stricturing CD. No evidence was found to support any association between family history of IBD and B2/B3 outcomes.[7, 38, 39]

Disease severity at diagnosis as a predictor for progression to stricturing or penetrating disease was examined in multiple studies. In a study of 63 children, endoscopic activity (assessed using the Simple Endoscopic Score) was the only factor independently associated with a risk of progression to stricturing/penetrating disease (adjusted risk ratio 3.20, 95% CI 1.04–4.91); clinical disease activity (pediatric CD activity index [PCDAI]) and histopathology (Global Histology Activity Score) were not associated with progression to stricturing or penetrating disease. Of note, in this study, B2/B3 complications were considered part of a composite outcome that included perianal disease and anti-tumor necrosis factor (TNF) use.[37] Clinical activity (PCDAI), biochemical activity (C-reactive protein [CRP]), hemoglobin, and albumin were not significantly associated with B2/B3 complications in a retrospective study of 215 children with ≥10 years of follow-up.[39] Consistent with these results, PCDAI and CRP were not associated with B2/B3 complications in an IBD study (200 with CD) and a study of 36 children with stricturing CD.[7, 38] However, conflicting results were reported from a study evaluating the impact of the TNF-α 308 G/A promoter SNP in children with IBD, which found that higher PCDAI and CRP were significantly associated with stenosing/penetrating complications.[40]

The presence of granulomas was examined in multiple studies and not found to be associated with B2/B3 complications.[32-34, 37, 39, 52]

Similarly, three studies examined upper GI involvement and identified an association with the combined outcome of B2/B3 complications.[37, 38, 40] Extraintestinal manifestations[38, 39] were found to be unrelated to disease progression.

One study examined diagnostic delay and found that it was not related to disease progression.[39]

Statement 2.8. Older age at CD onset may be associated with an increased risk of developing perianal disease (97% agreement).

A significant association between older age at diagnosis and perianal disease development was observed in two studies. A retrospective analysis of a prospective observational cohort derived from the ImproveCareNow Network, which included 7,076 children with CD, found that whereas the overall odds of developing perianal disease did not differ across age groups, older age at diagnosis was associated with a greater risk of developing perianal disease among Asian children (OR 1.14, P=.01).[53] Additionally, significantly more children >10 years at CD onset developed perianal disease sooner after diagnosis than those who were ≤10 years of age of CD onset (HR 1.13, P<.001). This was confirmed in a study of 215 children with >10 years of follow-up, where older age at diagnosis was associated with perianal disease development (HR 1.19, 95% CI 1.002–1.42).[39] Furthermore, Gupta et al. reported a trend toward perianal disease development in older children (>5 years vs 0–5 years) (HR 2.24, 95% CI 0.97–5.19, P=.06).[35] In contrast, patients with and without perianal disease did not differ significantly in age in the RISK study; however, the study analyzed patients at the time of presentation rather than perianal disease development over time.[36]

Statement 2.9. Children and adolescents of Black and South Asian ethnicity with CD are at a greater risk of developing perianal disease (92% agreement).

As discussed earlier, White children were at a significantly lower risk of developing perianal disease than non-White (HR 1.28, *P*<.001), Black children (adjusted OR 2.47, *P*=.017), or South Asian children.[43, 53] However, further analyses of the RISK study published since the consensus meeting did not identify ethnicity as a risk factor for perianal disease; this evidence was based on an assessment of relationships between nicotinamide adenine dinucleotide phosphate gene mutation and perianal disease.[54]

Statement 2.10. Bacterial serology and sex may be associated with the development of perianal disease; genetics, antineutrophil cytoplasmic antibody (ANCA) positivity, anthropometric parameters, disease location, disease behavior, extraintestinal manifestations, diagnostic delay, and disease activity do not predict the development of perianal disease (86% agreement).

Bacterial serological markers, including ASCA, ALCA, antimannobioside carbohydrate antibodies, and anti-L antibodies, were independently associated with the composite outcome of perianal disease and B2/B3 complications.[27] In the RISK study, although ASCA IgA and IgG, CBir1, granulocyte-macrophage colony-stimulating factor, and OmpC positivity were common in children with perianal disease at presentation, these serologic markers as predicters for perianal disease were not assessed.[36] No association was observed between ANCA positivity and the risk of perianal disease.[36, 55]

Sex as a risk factor for developing perianal disease was investigated in multiple studies. Adler et al. observed an increased risk of perianal disease in boys (OR 1.19, 95% CI 1.04–1.36), as well as a more rapid occurrence in boys (HR 1.16, 95% CI 1.04–1.30).[53] Similarly, in the RISK study, children with perianal disease at presentation were more likely to be boys.[36] However, sex was not associated with perianal disease in a study of 989 children with CD[51] or in a long-term study with a 10-year follow-up that included 215 children.[39]

Genetic predictors for perianal disease have also been investigated. In a single-center study that compared genotypes between childhood- and adulthood-onset IBD, *DLG5* rs2165047 was significantly associated with perianal disease in patients with childhood-onset CD (risk ratio, 2.4, 95% CI 1.4–4.0, *P*=.003).[50] In a study of 108 Korean children with CD, *TNFSF15* rs3810936 was significantly associated with perianal disease (59% of patients with the CT variant had perianal disease vs 20% with the TT variant, *P*=.029).[56] Other genes have been investigated (*NOD2/CARD15*,[14, 15, 19, 21, 22, 47, 48, 50] *TNF*,[57] *MDR1*,[57] *TLR4*,[50] *OCTN*,[50] *IRGM*,[19, 48, 58] *ULK1*[48], and *ATG16L1*)[19, 48] and did not correlate with perianal disease.

Anthropometric variables have been examined as potential risk factors for perianal disease. In a retrospective analysis of a prospective observational study of 7,076 children with CD, BMI, weight, height, and height velocity did not predict the development of perianal disease.[53] Similarly, BMI was not associated with perianal disease in a retrospective study of childhood-onset CD with at least 10 years' follow-up.[39]

Disease location,[36, 39, 53] disease behavior,[39] extraintestinal presentation,[39] delay in diagnosis,[39] and disease activity (PCDAI or PGA)[36, 39, 53] were not associated with perianal disease in any identified studies.

Statement 2.11. Male sex, younger age at disease onset, and isolated small bowel disease may be associated with a greater risk of linear growth impairment (100% agreement).

Several large studies have identified an association between male sex and impaired growth. Gupta et al. reported that girls were at lower risk for growth failure (height-for-age or height velocity <5th percentile) (HR 0.28, 95% CI 0.12–0.63), and that the cumulative incidence of growth failure was lower in girls (4%) than in boys (13%).[51] Two studies of patients with childhood-onset CD reported that boys were at significantly higher risk for growth failure, and in one IBD study (211 with CD), a trend toward an association between male sex and final adult height was noted.[59-61]

Age at disease onset was investigated as a predictor for linear growth impairment in multiple studies with inconsistent results, possibly owing to the variable definition of growth failure. In a Swiss IBD study, transient growth impairment (height z-score below –1.64 on more than one occasion) was significantly associated with younger age. The risk for transient growth failure was almost seven times higher in children aged 2–11.6 years (than those aged 14.6–18 years) and 5.4 times higher in children aged 11.8–14 years (than those in the older reference group). However, no association between age and permanent growth impairment was observed.[62] In a retrospective study of 87 children, growth retardation (height z-score) was linked to younger age of onset, and for every extra year after disease onset, the mean height z-score nadir increased an average of 0.1 SD.[63] Furthermore, a French registry study of 261 patients and a study of 537 patients with childhood-onset CD also identified younger age at diagnosis as predictive of growth retardation (height, weight, and BMI in both studies).[60, 64] Of

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note, age was positively associated with height velocity in a multivariable analysis in a retrospective study of 116 children followed up to 15.4 years.[65] In contrast, multiple studies failed to establish any link between age of CD onset and growth failure, including a registry study of 989 children with CD.[35, 51, 61, 66]

An association between small bowel disease and growth impairment was observed across multiple studies. In a study of 87 children, absence of ileal disease (P=.02) and presence of colonic disease (P=.004) were predictive of absence of growth retardation (height, weight, and BMI).[63] In a retrospective study of 123 patients with childhood-onset CD, children with jejunal disease had significantly lower mean height standard deviation scores (SDSs) than those without jejunal disease (–0.70 vs –0.15, respectively, P=.034).[59] In another study of 93 patients with childhood-onset CD, ileal location was significantly associated with height retardation at disease onset and the lowest z-score during follow-up.[67] There are, however, a number of studies that found no association between disease location and growth outcomes,[9, 25, 62, 64, 68] although some study results might be confounded by the use of steroids and growth failure as a composite outcome with progression to complicated CD or surgery.[25, 62, 64]

Statement 2.12. More active disease (assessed at baseline or over time) predicts linear growth impairment (92% agreement).

Both clinical and biochemical disease activity were assessed as predictors for linear growth impairment. In a study of 53 children with IBD stratified by growth impairment (temporary, permanent, or no impairment), significantly higher PCDAI scores were noted in patients with transient or permanent growth impairment than in those with no impairment (P=.06) in the CD

subgroup.[66] Similarly, severe disease (≥1 of cumulative hospitalization time >14 days, steroid use, second-line therapy use, or immunosuppressive use) was associated with growth failure (z-score below –2) in multivariable analysis for both height (OR 6.2, 95% CI 2.23–17.06) and weight in another study (OR 4.52, 95% CI 1.44–14.24).[67]

Multiple studies demonstrated an association between higher erythrocyte sedimentation rate (ESR) and linear growth impairment,[61, 65, 69] with another showing a positive association between ESR and delay in the age of the pubertal growth spurt.[70] However, CRP and albumin were not linked to linear growth,[65, 66, 69] and growth impairment was not related to serum interleukin-6 levels.[66] In contrast, higher baseline interleukin-6 levels and PCDAI scores at baseline were associated with greater increases in fat-free mass over 2 years.[71] Insulin-like growth factor-1 and insulin-like growth factor binding protein 3 levels were not associated with transient or permanent growth impairment.[66]

Statement 2.13. Diagnostic delay is a risk factor for linear growth impairment (92% agreement).

The interval between symptom onset and diagnosis was negatively associated with height SDS at diagnosis, suggesting that a shorter time to diagnosis is associated with improved height at presentation.[59] A similar trend was observed in a study of 1,456 children with CD, where growth failure was observed in 9.4% of children diagnosed within 3 months, 15.7% of children diagnosed at 3–6 months, and 22.3% of children diagnosed >6 months after symptom onset (*P*<.001).[72] Of note, two studies of children with IBD did not find any association between diagnostic delay and height outcomes.[61, 73]

Statement 2.14. *NOD2/CARD15* **polymorphisms may be associated with low weight, and extraintestinal manifestations may be associated with linear growth impairment; pubertal status at disease onset, family history of IBD, ethnicity, gestational age, upper GI tract involvement, oral involvement, granulomas, disease behavior, perianal disease, and presenting symptoms do not predict linear growth impairment** (94% agreement).

NOD2/CARD15 as a risk factor for growth impairment was examined in multiple studies yielding conflicting results. One study found that a higher proportion of children with ≥1 *NOD2/CARD15* variants were in the lowest weight and height percentiles compared with children without a variant (weight 75% vs 20%, OR 3.7, 95% CI 1.8–7.5; height 50% vs 16%, OR 5.2, 95% CI 1.7–16), although a link with BMI was not found.[16] In contrast, *NOD2* was significantly associated only with underweight (BMI <10th percentile) at 1 year (*P*=.012), but not with growth failure (inappropriate growth velocity for age) at 1 year or short stature (height <3rd percentile) at maximum follow-up.[21] No link was observed between *NOD2* mutations and growth retardation (*z*-score < −1) or growth failure (*z*-score < −2) at onset, or weight or height nadir over follow-up.[67]

Extraintestinal manifestations as a potential predictor for impaired linear growth were investigated across three studies. In a registry study of 261 patients with childhood-onset CD, extraintestinal manifestations at diagnosis were significantly associated with height at maximal follow-up.[60] In a study of 537 patients with childhood-onset CD, extraintestinal manifestations were linked to growth impairment as part of a composite outcome of disabling CD.[64] In

contrast, in a prospective analysis of 295 patients with childhood-onset IBD (211 with CD),

extraintestinal manifestations were not associated with final adult height.[61]

Two studies examined CD onset during puberty as a predictor for impaired growth.

Although height SDSs were significantly lower in children with prepuberty-onset CD than in

those with CD onset during puberty ($P<.05$), the difference was not significant after controlling

for parental height. Furthermore, patients who had used corticosteroids during puberty were

significantly shorter than patients who had not ($P=.005$), which holds true when corrected for

target height ($P=.007$).[68] Similarly, in a study of 221 children with CD, prepubertal disease onset

was associated with more permanent growth impairment, although the significance was lost

during a multivariable analysis.[62]

There was no evidence supporting a link between family history of IBD and growth

impairment in a retrospective cohort study (n=221), a prospective analysis (n=211), and a

Belgium registry study (n=255) in patients with childhood-onset CD.[9, 61, 62] Similarly, there is no

evidence to support that ethnicity predicts growth impairment, from the results of a

retrospective cohort study (n=221), a prospective analysis (n=211), and a retrospective medical

record analysis of an IBD cohort (n=245).[30, 61, 62] In addition, in the Belgium registry study, no

significant association between gestational age and BMI and height at follow-up was found.[9] No

association between upper GI involvement and growth outcomes was found across multiple

studies, including a retrospective study (n=221), a French registry study (n=261), a study of

children with IBD (n=54), a study of predictors for disabling CD (n=537), a study of genetic

predictors for growth retardation (n=93), and a prospective study of 45 newly diagnosed

patients with childhood-onset CD.[60, 62, 64, 66, 67, 74] A single study that investigated genetic

polymorphisms in 65 Korean children with CD found no link between oral involvement and impaired growth.[75] The presence of granulomas was not identified as a predictor for impaired growth, as examined in 45 patients with childhood-onset CD who were followed from diagnosis to attainment of final height.[34]

Disease behavior (stricturing and/or penetrating disease) as a predictor for growth impairment was examined in three studies. Although two studies, a retrospective cohort study in children receiving steroid treatment (n=221) and a Belgium registry study, did not report a link,[9, 62] one French registry study (n=261) found that nonstricturing, nonpenetrating behavior at diagnosis was significantly associated with lower weight at maximal follow-up in multivariable analysis (–0.98 SDS vs –0.54 SDS for stricturing and –0.59 SDS for penetrating disease, P=.02).[60]

Perianal disease as a predictor for growth impairment was investigated in two studies. In a study of 537 patients with childhood-onset CD with 5-year follow-up, perianal disease was significantly associated with impaired growth as a composite outcome with surgery (P=.05).[64] However, a prospective registry (ImageKids) analysis with follow-up of over 18 months did not find any link between perianal disease and anthropometrics.[76]

A study of 989 children with CD from the Pediatric IBD Consortium Registry did not observe any association between presenting symptoms and growth impairment.[51]

Statement 2.15. Low height, weight, and body mass index predict reduced BMD (98% agreement).

Bone health, as assessed by BMD, has consistently been linked with nutritional status (assessed by weight and/or BMI). In a study of children with IBD (17 with CD), 24% of patients with low lumbar areal BMD were underweight compared with 4% of those with normal BMD (*P*=.009).[77] In another study of children with IBD (58 with CD), BMI was lower in children with BMD *z*-scores < –1 than in those with a normal BMD at diagnosis, although no link was observed between change in BMI and BMD in the longitudinal component of the study.[78] Additionally, in a study of 27 children with CD, BMD at follow-up correlated with weight at follow-up, although significance was lost in multivariable analysis, and BMI was not associated with BMD.[79] In a study of 18 children with CD weight and BMI, SDSs were independently predictive of a better change in BMD SDS (*P*=.02 for weight SDS, and *P*=.03 for BMI SDS).[80] In a 2-year longitudinal study in 42 children with CD, fat-free mass and bone mineral content were correlated.[71] Additionally, in 85 children with CD, lean mass correlated with BMD in both boys and girls.[81] Consistent with these findings, a trend toward lower lean mass *z*-scores in children with low lumbar spine areal BMD (*P*=.05) was noted in a study of 40 children with CD.[77]

Statement 2.16. Higher clinical disease activity (assessed by Pediatric CD Activity Index [PCDAI]) at baseline and over time may predict reduced BMD (98% agreement).

Studies have reported conflicting results regarding disease activity at baseline and over time as a predictor of BMD outcomes.

In a study of 76 patients with CD (aged 5–21 years), lower PCDAI scores at the start of each observation interval and greater reductions in PCDAI over each interval were independently associated with greater improvements in trabecular BMD *z*-scores, although PCDAI was not

associated with changes in cortical BMD.[82] In a study of 18 children with CD treated with adalimumab, lower PCDAI at time of adalimumab initiation was independently predictive of an improvement in bone mineral apparent density (*P*=.02).[80] Mean PCDAI over the year preceding dual-energy X-ray absorptiometry assessment for bone loss was inversely correlated with lumbar spine areal BMD (*r*=–0.62, *P*<.001); additionally, patients with moderate-to-severe activity (PCDAI >30) had significantly lower BMD area *z*-scores than those in clinical remission for the preceding year (*P*=.03) in a study of 56 children with IBD (35 with CD).[83] In a cross-sectional study of 119 patients with CD (aged 5–25 years), PCDAI at the time of study visit and average PCDAI per year correlated with BMD.[84] Similarly, in a retrospective study of 85 children and 112 adults with CD, PCDAI scores were 5.8 points higher, on average, in patients with low BMD (*z*-score < –1) than in those with normal BMD (*P*=.03).[21]

In contrast, an association between PCDAI (baseline or change over time) and a change in bone parameters were not observed in a study of 78 patients with CD (aged 5–18 years at diagnosis).[85] Similarly, in a single study with children with IBD and three cross-sectional studies, PCDAI was associated with BMD.[78] Furthermore, PCDAI was not found to be associated with BMD in three cross-sectional studies.[77, 79, 86]

Statement 2.17. Sex, disease location, disease behavior, extraintestinal manifestations, granulomas, and perianal disease do not predict BMD (84% agreement).

Seven studies failed to find any link between sex and BMD, including a study in 85 patients with childhood-onset CD and 117 with adult-onset CD; a long-term study of 224 patients who were diagnosed with CD between the ages of 13 and 19; a prospective follow-up study of 47

children and adolescents (24 males) with IBD (17 with CD); a cross-sectional study of 40

patients with IBD; a longitudinal study of 27 children with CD (20 boys, 7 girls); a cross-sectional

study of 119 patients aged 5–25 years with CD; and a study of children with IBD (82 with CD).[21,

51, 77, 79, 84, 87, 88] However, in a prospective study of 76 patients (aged 5–21 years) with CD,

whereas girls experienced smaller increases in periosteal and cortical area *z*-scores, sex was not

related to change in trabecular or cortical BMD *z*-scores.[82] In contrast, in a longitudinal cohort

study of 144 children and adolescents with IBD (45 with CD), boys experienced a more

pronounced increase in BMD.[89]

A possible association between disease location and BMD was examined in three studies;

none of which described a significant association, including a study of 85 patients with

childhood-onset CD and 117 with adult-onset CD; a study of children with IBD (58 with CD); and

a longitudinal study of 27 children with CD.[21, 78, 79]

Associations between BMD outcomes and disease behavior or extraintestinal

manifestations were not identified in a study comparing adult-onset and childhood-onset CD.[21]

In addition, a cross-sectional study of 119 patients with CD (aged 5–25 years) did not report any

association between BMD outcomes and extraintestinal manifestations,[84] a longitudinal study

of 27 children with CD found no association between the presence of granulomas and BMD

outcomes,[79] and perianal involvement was not a predictive factor in a study of 119 CD patients

(aged 5–25 years).[84]

Prognostic Risk Factors for Chronically Active Inflammatory Pediatric CD

Statement 3.1. ASCA positivity may predict the need for more intensive therapy (89% agreement).

Three studies examined ASCA status as a predictor of the need for more intensive therapy in children with CD and reported inconsistent results.[7, 28, 90] Double positivity for ASCA predicted an aggressive disease course in Crohn's colitis (*P*=.024) and, marginally, the need for biologics (10/16 vs 5/17, *P*=.056).[28] In 37 CD patients, need for anti-TNF treatment was significantly associated with ASCA positivity.[90] The third study included only patients with stricturing disease (n=36) and found ASCA status not to be associated with partial or complete response to therapy (defined as disease behavior B1).[7]

Statement 3.2. Microscopic ileocolonic involvement at diagnosis may be associated with subsequent macroscopic ileocolonic disease (98% agreement).

In a long-term study of 212 patients with childhood-onset IBD (105 with CD), microscopic ileocolonic involvement at diagnosis was more frequent in patients with disease extent progression, which was defined as progression from L1, L2, or L4 to L3. Additionally, microscopic ileocolonic involvement was an independent predictor for macroscopic ileocolonic disease extension (HR 4.32, 95% CI 1.93–9.67, *P*<.001).[39]

Statement 3.3. Disease activity and disease behavior (ie, B2 and/or B3), but not age and sex, may predict more intensive therapies or a poor response to therapies; there is no strong evidence for a predictive value of ethnicity (83% agreement).

Three studies examined the correlation between PCDAI at diagnosis and the need for second-line therapy. Müller et al. reported a significant association between PCDAI at diagnosis and the need for an immunomodulator after 1 year of follow-up in a study of 270 children (*P*=.026).[91] The other two studies (n=57 and n=37 children with CD) did not find any correlation between PCDAI and second-line therapy.[92, 93]

Age as a predictor for more intensive therapy or a poor response to therapy was examined in 10 studies. Three retrospective studies reported that age at diagnosis was not significantly associated with the need for steroids or immunomodulators, or a partial or complete response to therapy.[7, 94, 95] Additionally, several IBD studies (three studies with 26, 93, and 993 children with CD, and two studies with 96 and 160 children with IBD) did not find any association between age at diagnosis and subsequent intensive therapy (including corticosteroids, immunomodulators, and biologics).[8, 93, 96-98] Conversely, two studies reported an association, including a prospective observational registry study at multiple centers in North America that included 1,928 children with IBD, which found that a greater proportion of children aged 1–5 years with CD (42.9%) were receiving corticosteroids and methotrexate than children older than 5 years.[99] The second study of 506 children found that a significantly greater proportion of younger patients (0–5 years) were receiving steroids at the latest follow-up than children older than 5 years (*P*<.05), with no significant difference noted for immunomodulators or biologics.[4]

Sex also was not a predictor for intensive therapy in four studies.[94, 96-98] Although one of the studies reported a significant association between male sex and a better response to steroids 30 days after initiation of treatment (n=87, OR 3.2, 95% CI 1.2–8.1), this was not maintained over time (n=82, OR 2.5, 95% CI 0.8–7.5).[94] Of the studies that failed to report any significant

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findings, two involved large cohorts with >900 children with CD,[35, 96] and two included ≤100

children with a mixed population.[97, 98]

Two studies identified an association between ethnicity and the need for intensive therapy

in IBD, but no sub-analyses of children with CD were conducted. One study reported a higher

need for corticosteroids and infliximab in Black children and a higher need for azathioprine

during the first 3 months in White children (n=245).[30] Another study reported that the use of

methotrexate, steroids, or adalimumab was significantly higher in South Asian children than in

White children.[43]

Statement 3.4. No strong evidence exists to identify predictive factors of future disease

activity or disease severity (81% agreement).

Three studies investigated predictive factors of future disease severity in children with CD,

two of which identified a link.[9, 55, 63] A multicenter study with 155 CD patients and a median

follow-up of 2.7 years identified L1 (P=.042) and L3 disease (P=.033) at diagnosis as significantly

related to disease severity at inclusion in a univariate analysis; however, in a subsequent

multiple regression analysis, only CRP was an independent predictor of disease activity.[9] The

second study found that, in childhood-onset CD (n=87), the TNF polymorphism 857C/T was

associated with a significantly lower risk for severe disease (>2 weeks of hospitalization, >4

weeks of use of steroids and infliximab, or surgery) (OR 0.32, 95% CI 0.18−0.56, P=.02), whereas

TNF 308G/A was associated with a trend toward more severe disease (OR 3.2, 95% CI 1.4−7.2,

P=.08).[63]

Although an association between autophagy-associated genes (*ATG16L1*, *IRGM*, *ULK1,* and *NOD2*) and disease behavior was possible, as they were identified using 12 SNPs in a study of 65 Korean CD patients with a mean follow-up of 4.73 years (±4.4 SDs), the study did not describe a significant association between disease behavior and any of the genes.[48] Similarly, a study of 102 children with IBD (64 with CD) failed to identify serum ANCA as a significant predictor for disease course (quiescent, mild, or severe) in children with CD.[55]

Statement 3.5. No strong evidence exists for predictors of disease relapse and the number of relapses (98% agreement).

Among six studies, there was no strong evidence to support any factors as predictors for relapse as the studies were limited by population size and retrospective study design.[8, 19, 29, 74, 75, 100]

ASCA IgA positivity was significantly associated with relapse in a study of 61 children (OR 2.9, 95% CI 1.33–6.35).[29] In a study of 160 children with IBD (72 with CD), a significantly higher incidence of relapse per patient per year was noted in children diagnosed at 5–10 years than in children diagnosed at 11–16 years (mean 1.4 ± 0.2 vs 0.85 ± 0.1, P=.05, OR 1.2, 95% CI 1.01–1.65).[8] In a retrospective study of 80 children with CD, a significant association between homozygosity of the ATG16L1 risk allele and relapse during the first year of disease (OR 1.2, P=.002, multivariate regression analysis) was reported.[19] In a study of 37 children with CD in clinical remission receiving maintenance therapy, there was a significantly increased risk for relapse after 1-year follow-up in children with a polymorphonuclear neutrophil CD64 index >1.0 compared with <1.0 (relapse rate 44% and 5%, respectively, P<.01).[100] Another study reported

that a growth delay at diagnosis was more frequent in children with a relapse; however, the study lends little support for growth delay as a predictor owing to the lack of a statistical comparison.[101] The presence of oral lesions and upper GI tract involvement at diagnosis were not associated with number of relapses.[74, 101]

Conversely, the rate of remission (PGA=0) was significantly higher in IBD unidentified than in CD at a median follow-up of 2.8 years (interquartile range 1.6–4.2 years) that included 250 children with CD, 287 children with ulcerative colitis, and 160 children with IBD unidentified.[102]

Statement 3.6. Stricturing and/or internal penetrating (B2/B3) phenotype and the presence of granulomas and increased visceral adipose tissue may predict hospitalizations; small bowel involvement, *TNF* polymorphisms, *NOD2* variants, and age do not predict hospitalization (88% agreement).

Predictors for hospitalization were investigated in seven studies; however, as they were mostly single-center studies, the factors identified are not reliable predictors for hospitalization. In a single-center study of 289 patients with childhood-onset CD with a median follow-up of 8.5 years (interquartile range 5.2–11.7 years), the presence of granulomas was associated with an increased risk for hospitalization (HR 1.43, 95% CI 1.0–2.0).[33] Another single-center retrospective study of 114 children with CD reported that an increase in visceral adipose tissue significantly increased risk of hospitalization (OR 1.9, 95% CI 1.2–3.4, *P*=.01), possibly owing to association with increased systemic inflammation.[103] In a retrospective single-center study, no significant difference in the incidence of hospitalization was noted in children with (18 out of 23 children) or without (21 out of 36 children) proximal small bowel involvement.[104]

In a study of 87 children with CD with ≥1 year of follow-up, the presence of TNF polymorphisms did not significantly affect the duration of hospitalization.[63] In a study of 85 children with CD with ≥2 years of follow-up, *NOD2* variants were not predictive of more than 2 weeks' hospitalization per year.[21]

Two studies have reported that age is unlikely to be associated with an increased risk for hospitalization, although both studies were conducted in children with IBD. In a prospective multicenter observational study of 1,928 children, no difference was observed in the risk for hospitalization at baseline, 1-year follow-up, or 5-year follow-up between three subgroups of children categorized by age at diagnosis (0–5 years, 6–10 years, 11–16 years).[99] The second study reported no significant difference in risk of hospitalization (estimated number of unplanned inpatient and outpatient days) between children diagnosed at 5–10 years and those diagnosed at 11–16 years.[8]

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Table 1S. Characteristics of Studies Examining Predictor-Outcome Combinations Not Included in Meta-Analysis

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Adler (2017)	Prospective,[1] multicenter	6679 pediatric CD Median 12.4 (IQR 9.9–14.8) y, 59% M	Weight, height, BMI and height velocity z-score, sPCDAI, PGA Sex, age, race/ethnicity, geographic regions Disease location (lower and upper)	Perianal disease	Median 1.3 (IQR 0.5–2.6) y
Alemzadeh (2002)	Retrospective, single center (questionnaire)	135 CD (64 pediatric) 33% M	Disease location, age	Adult height (SDS, height minus target height)	N/A
Aloi (2014)	Prospective, multicenter	506 early-onset IBD Mean 10.2 (range 0.8–18.3) y, 54% M	Age (0–5 vs 6–11 vs 12–18 y)	Surgery (any resection) Intensified treatment (on steroids at last follow-up)	Mean 40 (range 6–50) mo
Crocco (2012)	Retrospective, single center	45 pediatric CD 10.9–12.6 y, 58% M	Upper GIT	PCDAI, number of relapses Height and weight percentiles at end of F/U Immunosuppressive medication	Mean 3 (range 2–4) y
Cucchiara (2007) JPGN	Retrospective, multicenter	200 pediatric CD Mean 12 (SD 4) y, 49% M	Genetics (TNF variant, MDR1)	Surgery (resection), disease behavior, perianal fistulizing disease, medication use	9 (SD 7) y
De Matos (2008)	Retrospective, single center	184 pediatric CD Median 12.6 (range 1.06–19.7) y, 60% M	Granuloma	Perianal disease (deep fissure, fistula, abscess) Infliximab, surgery (resection, stricturoplasty) B2, B3	Median 3 (range 0.4–8.7) y
De Ridder (2007)	Retrospective, single center	103 pediatric CD Mean 14 (range 6–18) y, 56% M	Genetics (NOD2/CARD15 variants, TLR4, OCTN, DLG5)	B2/B3, surgery, perianal disease	N/A
Dubner (2009)	Retrospective, single center	78 pediatric CD Mean 12.7 (range 5.5–18) y, 56% M	Tanner stage (1–2 vs 3–5), PCDAI Baseline trabecular BMD z-score, muscle CSA z-score	BMD (change in trabecular and cortical BMD, change in bone strength)	6 mo
Duchatellier (2016)	Retrospective, single center	221 pediatric CD Mean 12.4 (SD 3.2) y, 54% M	Age (2–11.6, 11.8–14 vs >14.6 y), prepubertal status, sex Disease behavior, location, upper GIT, disease activity Family history of IBD, race	Transient growth impairment (height z-score <5th percentile) Permanent growth impairment (adult height >8.5 cm less than expected)	Mean 4.9 (SD 2.9) y
Freeman (2004)	Prospective, multicenter (database)	224 pediatric CD <20 y, 43% M	Sex Disease location, behavior	B2, B3, surgery (resection) Medication use	Mean 12.2 y
Freeman (2007)	Prospective, multicenter (database)	114 pediatric CD <17 y, 46% M	Granuloma	B2 B3	Mean >10 y
Gasparetto (2016)	Retrospective, multicenter	160 pediatric IBD (mixed IBD cohort) 52% M	Age (5–10 vs 11–16 y)	Surgery, hospitalization Intensified treatment (anti-TNF), number of relapses	Median 1.2–4.2 y
Guariso (2010)	Retrospective, single center	67 pediatric CD (mixed IBD cohort)	Growth deficiency	Number of relapses	Mean 4.8 years
Gupta (2004)	Retrospective, single center	123 pediatric CD Mean 11.8–11.9 (SD 2.4–2.9) y, 53% M	Sex	BMD (increase/loss spine BMD corresponding to highest/lowest quartiles)	Min 3.4 y
Gupta (2007)	Retrospective, multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57% M	Sex Presenting IBD symptoms	B2, B3 (fistula, abscess), perianal fissure Medication use Growth failure (height-for-age or height velocity <5th percentile) Compression fracture or osteopenia/osteoporosis	Median 2.8 y (range 1 d – 16.7 y)
Hussey (2011)	Retrospective, single center	21 pediatric CD Mean 15.7 (SD 1.98) y, 71% M	Oral manifestations	Growth (weight and height z-scores), relapse	Mean 55 (SD 22) mo
Ideström (2014)	Retrospective, single	45 pediatric CD	Granuloma	Growth (final adult height SDS adjusted for target height),	Median 12.3

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	center	Median 10.3 y, 60% M		disease behavior, surgery	(range 9.3–18) y
Jakobsen (2011)	Retrospective, single center	105 pediatric CD (mixed IBD cohort) Median 12.8 (0.4–14.9) y, M 54%	Age, sex	Medication use	Median 4.9 (IQR 3.9–7.6) y
Jakobstein (2006)	Retrospective, single center	57 pediatric CD patients	PCDAI at diagnosis	Medication use	Min 6 mo
Laakso (2014)	Prospective, single center	17 pediatric CD Median 14.5 (range 5.1–19.2) y, 51% M	Height-for-age z-score, weight (under/over/normal), sex, disease activity	BMD (lumbar spine areal BMD, height-adjusted whole body less head bone mineral content)	Median 5.4 (4.9–6.3) y
Latiano (2009)	Retrospective, multicenter	265 pediatric CD <19 y, 57% M	Genetics (IRGM variant)	Perianal disease, internal fistulizing disease	Mean 8 (SD 7) y
Ledder (2014)	Retrospective, multicenter	47 pediatric CD (mixed IBD cohort)	Age (<6 vs 6–17 y)	Medication use	Mean 4.5–4.9 y
Lee (2010)	Prospective, multicenter	211 pediatric CD (mixed IBD cohort) Mean 13.9 (SD 3.9) y, 57% M	Sex, age, diagnostic delay, EIM, family history of IBD, ethnicity Parental height, minimum height z-score during F/U ESR, ethnicity	Growth (final adult height)	Mean 2.3 y
Lee (2012)	Cross-sectional, multicenter	993 pediatric CD Median 16.6 (IQR 14.2–18.6) y (M), 16.8 (14.4–18.7) (F), 57% M	Sex, age	Growth (BMI z-score, height velocity), medication use	Median 16.6 mo
Lee (2014)	Retrospective single center	54 pediatric CD Mean 15–16 (SD 2–4) y, 67% M	Sex, age, SB disease, disease activity (clinical, biomarker), upper GIT	Growth (height-for-age z-score <5th percentile, transient or permanent)	N/A
Lee (2015)	Retrospective, multicenter	108 pediatric CD Mean 13 (SD 2.8) y, 69% M	Genetics (TNFSF15) Disease behavior	Perianal disease, medication use (TNFα)	Mean 2.7 (SD 2.2) y
Levine (2005)	Retrospective, multicenter	87 pediatric CD Mean 12.1 (SD 3.7) y, 63% M	Genetics (TNF promoter polymorphisms), sex, age, disease location	Growth (weight and height z-score nadir, growth retardation – z-score <−1, failure – z-score <−2) Disease activity/severity (PCDAI, PGA, hospitalization), second-line therapy (need for surgery or infliximab)	Min 1 y
Lopes (2008)	Retrospective, single center	14 pediatric CD (mixed IBD cohort) Mean 11.8 (SD 4.1) y, 52% M	Age, height-for-age z-score, BMI z-score	BMD (lumbar z-score <−2)	N/A
Malik (2012)	Retrospective, single center	116 pediatric CD Mean age 10.8 (range 2.9–15.5) y, 59% M	Age, disease activity (biomarker), weight SDS	Growth (height SDS, height velocity SDS)	Mean 4.6
Mason (2011)	Retrospective, single center	41 pediatric CD Median 12.8 (range 5.3–14.5) y (M), 11.6 (8.5–12.8) y (F), 73% M	Disease activity (biomarker)	Growth (peak height velocity SDS, height SDS)	Min 2 y
Mason (2015)	Prospective, single center	45 pediatric CD Median 13.4 (range 10–16.6) y	Disease activity (biomarker)	Growth (height and height velocity SDS, change in height SDS)	12 mo
Minar (2014)	Retrospective, single center	83 pediatric CD Median 15 (range 1–24) y, 61% M	Neutrophil CD64 index	Clinical relapse	12 mo
Mossop (2008)	Retrospective, single center	93 pediatric CD (mixed IBD cohort)	Sex, age	Medication use (immune modulator)	3.9 (0.5–10.6) y
Muller 2016	Prospective, multicenter	240 pediatric CD (mixed IBD cohort) Median 14.2 (11.8–16.1) y, 56% M	PCDAI at diagnosis	Medication use (anti-TNFα)	12 mo
Newby (2008)	Retrospective, multicenter	116 pediatric CD (mixed IBD cohort)	Diagnostic delay Age, sex	Growth (height SDS) Surgery	Mean 3.4 y (CD)

		Median 11.8 (range 4–16) y, 72% M			
Olbjorn (2014)	Retrospective, multicenter	37 pediatric CD Median 13 y, 56% M	PCDAI at diagnosis B3	Medication use (anti-TNFα)	Median 20 (range 12–24) mo
Olbjorn (2017)	Retrospective, multicenter	37 pediatric CD Median 13.9 y, 57% M	ASCA	Medication use (anti-TNFα)	Median 20 (range 12–24) mo
Oliva-Hemker (2015)	Prospective, multicenter	1928 pediatric IBD, median age 12.4, 56% M	Age (1–5 vs 6–10 vs 11–16 y)	Medication use Hospitalization	Median 3.25 y
Olives (1997)	Retrospective, multicenter	64 pediatric CD (mixed IBD cohort) Mean 10.9 (SD 2.1) y (CD), 56% M	ANCA	Disease activity (clinical, endoscopic), perianal disease	N/A
Paganelli (2007)	Prospective, single center	35 pediatric CD Mean 13.5 (range 5–19) y, 63% M	Anthropometrics (height, BMI z-scores) Disease activity (PCDAI, biomarker, including cytokine levels) Bone age, pubertal stage	BMD (areal BMD, bone mineral apparent density z-score)	N/A
Pichler (2015)	Retrospective, single center	18 pediatric CD Median 7.8 y (range 2.9–15.3), 28% M	Anthropometrics (BMI, weight, height SDS) Disease activity (PCDAI)	BMD (areal BMD, bone mineral apparent density SDS)	1 y
Rothschild (2017)	Retrospective, single center	289 pediatric CD Median 14.2 y, 68% M	Granulomas	Hospitalization, intestinal resection, B2/B3	Median 8.5 y
Russell (2009)	Retrospective	197 pediatric CD Median 11.25 (IQR 8.75–13) y, 58% M	ASCA	Surgery	N/A
Samson (2010)	Prospective, single center	27 pediatric CD Median 12.5 (IQR 7.2–15.9) y, 74% M	Weight, height, growth rate over 1 y SDS, BMI percentile Disease activity, location Age, sex, granulomas	BMD (change in BMD z-score per chronological and bone age)	1 y
Sawczenko (2006)	Retrospective, multicenter	123 pediatric CD Mean 12.2 (SD 2.8) y, 53% M	Diagnostic delay, prepubertal status, age, sex, disease location, mid-parental height z-scores	Growth (final height SDS, when growth velocity <1 cm/y x at least 6 mo)	Mean 10.4 (SD 7.1) y
Schmidt (2009)	Cross-sectional, multicenter	45 pediatric CD 6–19 y, 65% M	Anthropometrics (weight, height, BMI) Age, sex, disease duration	BMD (BMD z-score <-2)	2 y
Schmidt (2012)	Cross-sectional, multicenter	37 pediatric CD (mixed IBD cohort) 6–19 y, 64% M	Sex, age, height (change in z-score)	BMD (change)	2 y
Semeao (1999)	Retrospective, single center	119 pediatric CD Mean 16.2 (SD 4.1), 61% M	Anthropometrics (weight, height z-score) Sex, age, EIM, perianal disease Disease activity/severity (PCDAI, biomarker, hospitalization), location	BMD (z-score <–1)	N/A
Setty-Shah (2016)	Cross-sectional	15 pediatric CD Mean 13.7 (SD 2.6) y, 62% M	Anthropometrics (weight, height, BMI z-score) Disease activity (PCDAI)	BMD (z-score)	N/A
Stordal (2004)	Prospective, multicenter	16 CD (mixed IBD cohort)	Age	Surgery (for B2 complications)	5 y
Sylvester (2007)	Prospective, multicenter	48 pediatric CD Mean 13 (SD 3) y	Anthropometrics (change in BMI, height) Disease activity (PCDAI), location	BMD (change in z-score)	2 y
Sylvester (2009)	Prospective, multicenter	42 pediatric CD Mean 12.6 (SD 2.8) y, 69% M	Nutritional status (fat-free mass) Disease activity (PCDAI, biomarker)	BMD (change bone mineral content) Change in fat-free mass z-score	2 y
Timmer (2011)	Retrospective, multicenter	1,456 pediatric CD <18 y, 56% M	Diagnostic delay	Growth failure (as per treating physician)	N/A
Tsampalieros (2013)	Prospective, single center	76 pediatric CD Mean 12.6 (SD 2.8) y, 55% M	Age, sex, disease activity (PCDAI)	BMD (change in trabecular, cortical BMD z-score, change in cortical area z-score)	Median 42 (range 23–54) mo

					Min 12 mo
Tung (2006)	Retrospective, multicenter	26 pediatric CD (mixed IBD cohort) 15.2 (8.4–18.8) y, 62% M	Age, sex	Medication use	12 mo
Uko (2014)	Retrospective, single center	101 pediatric CD (mixed IBD cohort) Median 16 (14–17) y, 55% M	Visceral adipose tissue	Hospitalization Surgery	Min 12 mo
Vasseur (2010)	Retrospective, multicenter	261 pediatric CD Median 13 (IQR 11.2–15.4) y, 60% M	Age, sex, EIM, upper GIT	Height, weight, BMI	Median 73 (IQR 46–114) mo Min 2 y
Wine (2004)	Retrospective, multicenter	93 pediatric CD Mean 12.1 (SD 3.6) y, 60% M	Genetics (NOD2 variant) Disease activity, location	Weight, height failure (z-score <–2)	Min 1 y
Zwintscher (2014)	Retrospective, multicenter	7846 pediatric CD Mean 16 y, 61% M	Obesity (as per ICD-9 codes)	Severe disease, including GI hemorrhage, perforation, complex fistulas, surgery	N/A

ANCA, antineutrophil cytoplasmic antibodies; ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMD, bone mineral density; BMI, body mass index; CD, Crohn's disease; CSA, cross-sectional area; EIM, extraintestinal manifestation; ESR, erythrocyte sedimentation rate; F, female; F/U, follow-up; mo, months; GIT, gastrointestinal tract; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; IQR, interquartile range; M, male; N/A, not available; PCDAI, pediatric Crohn's Disease Activity Index; PGA, physician global assessment; SD, standard deviation; sPCDAI, short pediatric Crohn's Disease Activity Index; SB, small bowel; SDS, standard deviation score; TNF, tumor necrosis factor; y, year
[1] Retrospective analysis of prospectively collected data

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Table 2S. Risk of Bias Studies Examining Predictor-Outcome Combinations Not Included in Meta-Analysis

Study	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Adler (2017)	1	1	1	1	2	1	1	1	9
Alemzadeh (2002)	1	1	0	1	0	0	1	1	5
Aloi (2014)	1	1	1	1	0	1	1	1	7
Crocco (2012)	1	1	1	1	0	1	1	1	7
Cucchiara (2007)	1	1	0	0	0	1	1	1	5
De Matos (2008)	1	1	1	1	0	1	1	1	7
De Ridder (2007)	1	1	1	0	0	1	0	1	5
Dubner (2009)	1	1	1	1	2	1	0	1	8
Duchatellier (2016)	1	1	1	1	2	1	1	0	8
Freeman (2004)	1	1	1	0	1	1	1	1	7
Freeman (2007)	0	0	1	0	0	1	1	1	4
Gasparetto (2016)	1	1	1	1	2	1	1	1	9
Guariso (2010)	1	1	1	1	0	1	1	0	6
Gupta (2004)	1	1	1	1	1	1	1	1	8
Gupta (2007)	1	1	1	0	1	0	1	1	6
Hussey (2011)	1	1	1	0	0	1	1	0	5
Idestrom (2014)	1	1	1	0	0	1	1	1	6
Jakobsen (2011)	1	1	1	1	2	1	1	1	9
Jakobstein (2006)	1	1	1	1	0	1	0	0	5
Laakso (2014)	0	0	1	0	1	1	1	1	5
Latiano (2009)	1	1	1	0	0	0	1	1	5
Ledder (2014)	1	1	1	1	0	1	1	1	8
Lee (2010)	0	0	1	0	2	1	1	1	6
Lee (2012)	1	1	1	0	1	1	0	1	6
Lee (2014)	1	1	1	0	0	1	0	1	5
Lee (2015)	1	1	1	0	0	1	1	1	6
Levine (2005)	1	1	1	1	2	1	0	1	8
Lopes (2008)	0	0	1	0	0	1	0	1	3
Malik (2012)	1	1	1	1	0	1	1	1	7
Mason (2011)	1	1	1	0	0	1	1	1	6
Mason (2015)	1	1	1	0	0	1	0	1	5
Minar (2014)	1	1	1	1	1	1	1	1	8
Mossop (2008)	1	1	1	1	0	1	1	1	8
Muller (2016)	1	1	1	1	1	1	1	1	8
Newby (2008)	1	1	1	0	0	1	1	1	6
Oliva-Hemker (2015)	1	1	1	1	0	1	1	1	7
Olbjorn (2014)	1	1	1	1	0	1	1	1	7
Olbjorn (2017)	1	1	1	1	0	1	1	1	7
Olives (1997)	1	1	1	0	0	1	0	1	5

Paganelli (2007)	1	1	1	1	2	1	0	1	8
Pichler (2015)	0	0	1	1	1	1	1	1	6
Rothschild (2017)	1	1	1	1	0	1	1	1	7
Russel (2009)	1	1	1	1	0	1	0	0	5
Samson (2010)	1	1	1	1	1	1	1	0	7
Sawczenko (2006)	1	1	1	1	0	1	1	0	6
Schmidt (2009)	1	1	1	1	1	1	1	0	7
Schmidt (2012)	1	1	1	1	2	1	1	0	8
Semeao (1999)	0	1	1	0	2	1	0	1	6
Setty-Shah (2016)	0	0	1	0	0	1	0	1	2
Stordal (2004)	0	1	1	1	0	1	1	0	5
Sylvester (2007)	1	1	1	1	0	1	1	0	6
Sylvester (2009)	1	1	1	1	0	1	1	0	6
Timmer (2011)	1	1	0	1	0	0	1	1	5
Tsampalieros (2013)	0	1	1	1	0	1	1	0	5
Tung (2006)	1	1	1	1	0	1	1	0	6
Uko (2014)	1	1	1	1	2	1	1	1	9
Vasseur (2010)	1	1	1	1	2	1	1	0	8
Wine (2004)	1	1	1	1	2	1	1	0	8
Zwintscher (2014)	1	1	1	0	2	1	0	1	7

Based on Newcastle-Ottawa Scale

All columns 0 or 1 stars except comparability (0 to 2), last column = total # of stars