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Predicting Outcomes in Pediatric Crohn's Disease for Management Optimization: Systematic Review and Consensus Statements From the Pediatric Inflammatory Bowel Disease–Ahead Program

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BACKGROUND & 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* antibody status. Isolated colonic disease was associated with fewer surgeries. Older age at presentation, small bowel disease, serology (anti-*Saccharomyces cerevisiae* antibody, 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.

Pediatric-onset Crohn's disease (CD) is heterogeneous. Beyond stricturing (B2), internal penetrating (B3) disease, and need for surgery, complications in

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Abbreviations used in this paper: **aHR, adjusted hazard ratio; ANCA, antineutrophil cytoplasmic antibodies; ASCA, anti–*Saccharomyces cerevisiae* antibodies; B2, stricturing behavior; B2/B3, stricturing and/or internal penetrating behavior; B3, internal penetrating behavior; BMD, bone mineral density; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; IBD, inflammatory bowel disease; OR, odds ratio; PCDAI, Pediatric Crohn's Disease Activity Index; PIBD, pediatric inflammatory bowel disease; SC, steering committee; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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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, the 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 reported here.

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 2 cochairs (A.M.G. and D.T.) 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 by using meta-analysis, where possible. Finally, after 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 1 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 articles 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 Supplementary 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 (M.A., A.R., E.O.M., and N.C.) reviewed all abstracts in duplicate to determine which full texts to retrieve. Full texts were also reviewed in duplicate (M.A., A.R., E.O.M., and N.C.). At both stages, disagreements were resolved by consensus with input from 1 of the principal investigators (A.M.G., D.T.).

Data were extracted independently and in duplicate (M.A., A.R., and E.O.M.) 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 2 $\times$ 2 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 the results were unadjusted or adjusted. Otherwise, studies were reviewed qualitatively for whether they showed 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 (M.A., A.R., E.O.M.) using the Newcastle-Ottawa Scale, as appropriate for observational studies (no randomized controlled trials were identified). The Newcastle-Ottawa Scale is based on 8 factors (total score range, 0–9) across 3 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 believed 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 (CIs). Results were pooled by using random effects in all cases, because we expected at least some clinical heterogeneity among studies. This was accomplished by 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 of $\leq$40%).[2] We had planned to assess publication bias graphically using funnel plots, but this was not possible because of insufficient study numbers (<10) per outcome. Analyses were performed using R, version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

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, Spain, where the statements were finalized.

At the final February 2018 consensus meeting in Vienna, Austria, 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 1 positive study was available or when there was more than 1 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 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram in Supplementary Figure 1. A total of 101 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 Tables 1 and 2, respectively. The equivalent data for studies examining predictor-outcome combinations not included in meta-analyses are shown in Supplementary Tables 1 and 2. All included studies were observational. Thirty-one studies were high quality, 45 were moderate quality, and 25 were 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 the Supplementary 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, 4 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 3 showed a significant association.[4,6,8,14,16] Two meta-analyzable studies showed 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 = 1438; $I^2 = 0\%$) (Figure 2*A*).[6,16] One of the 2 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 = 2289; $I^2 = 24\%$) (Figure 2*B*).[5,6,10,16] The pooled unadjusted OR from a smaller analysis of 2 studies with no heterogeneity further supported this (pooled OR, 0.30; 95% CI, 0.15–0.58; $P = .0003$; n = 621; $I^2 = 0\%$) (Supplementary Figure 2*A*).[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, 3 reported disease location to not be a significant risk factor.[7–9] Attard et al[19] 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 2 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 6 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 = 2780; $I^2 = 22\%$) (Figure 2*C*). A smaller analysis of 5 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 = 4256; $I^2 = 36\%$) (Supplementary Figure 2*B*).[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,[21] also not included in the meta-analysis, reported an increased risk for female patients in a multivariable analysis (HR, 1.69; 95% CI, 1.07–2.17; $P < .009$). The 2 remaining

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

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Aloi et al (2013)[11]	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 y (SD, 4.12)
Ammoury and Pfefferkorn (2011)[20]	Retrospective, single center	81 pediatric CD Mean: 11.6 y (range, 4–18 y) 63% M	Esophageal involvement	Surgery	Mean: 3.5 y (range, 6 mo to 10 y)
Amre et al (2006)[17]	Retrospective, single center	139 pediatric CD Mean: 11.2 y (SD, 3.4) 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 y (SD, 3)
Attard et al (2004)[19]	Retrospective, single center	134 pediatric CD Mean: 12.0 y (SEM, 1.2)	Jejunoileitis	Surgery Hospitalization	N/A
Birimberg-Schwartz et al (2016)[33]	Retrospective, multicenter	406 pediatric IBD (mixed cohort) Mean: 10.5 y (SD, 3.9) 54% M	Serology (ASCA, pANCA)	Surgery Intensified treatment (biologic or calcineurin inhibitor)	Median: 2.8 y (IQR, 1.6–4.2)
Chhaya et al (2015)[12]	Retrospective, multicenter	1595 pediatric CD	Age (0–9 vs 10–13 vs 14–16 vs 17–24 y) Sex	Surgery (resection, strictureplasty, stoma creation)	Mean: 4.3 y
Cucchiara et al (2007)[22]	Retrospective, multicenter	200 pediatric CD Mean: 12 y (SD, 4) 58% M	Genetics (NOD2/CARD15 variant)	Surgery (resection)	Median: 2.8 y (range: 1 d to 16.7 y)
De Greef et al (2013)[8]	Retrospective, multicenter	155 pediatric CD Median: 12.5 y (range, 1.6–18) 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 follow-up PCDAI, PGA, surgery (IBD related), medication use	Median: 2.7 y (range, 0.3–8.2 y)
Desir et al (2004)[34]	Combined retrospective and prospective, single center	61 pediatric CD Mean: 10.7 y (SD, 3.4) 49% M	ASCA (IgA, IgG, positivity, and titer)	B3 (fistula or abscess) Surgery (small or large bowel) Relapse	Mean: 4.9 y (SD, 2.1)
Dubinsky et al (2006)[47]	Prospective, multicenter	167 pediatric CD Median: 12 y (range, 1–18 y) 47% M	ASCA, OmpC, I^2, and/or CBir1 Antibody sum score	B2 or B3	Median: 18 mo (range, 1–200 mo)

Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Dubinsky et al (2008)[21]	Prospective, multicenter	536 pediatric CD Median: 12 y (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 et al (2007)[35]	Retrospective, single center	137 pediatric CD, mixed cohort Mean: 12.6 y (SD, 4.1) 47% M (Black) Mean: 11.6 y (SD, 4.5) 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 y (SD, 3.0) (Black) Mean: 4.8 y (SD, 3.2) (White) (Growth at 1 y)
Fabian et al (2017)[41]	Retrospective, single center	63 pediatric CD Median: 12 y (range, 11–15 y) y 57% M	Age (continuous)	Complications (stricture that cannot be passed or with upstream dilatation, internal fistula or abscess, perianal fistula or anti–TNF-α use)	1 y
Ferraris et al (2006)[25]	Retrospective, multicenter	134 pediatric CD Median: 12 y (IQR: 9.5–13) 51% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (abdominal surgery)	N/A
Gupta et al (2006)[6]	Retrospective, multicenter	989 pediatric CD Mean: 11.5 y (SD, 3.8) 57% M	Sex, age (0–2, 3–5, 6–12, 13–17 y) Ethnicity (Caucasian, Black, Asian/Pacific Islander, Hispanic, other) Poor growth (at presentation, not further defined) Disease location, severity (PCDAI) granuloma, serologies	Surgery (partial SB resection, partial/total colectomy)	Mean: 3.6 y (SD, 3.1)
Gupta et al (2008)[39]	Retrospective (registry), multicenter	989 pediatric CD Mean: 11.5 y (SD, 3.8) 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 to 16.7 y)

Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Gupta et al (2010)[46]	Retrospective (registry), multicenter	989 pediatric CD Mean: 11.5 y (SD, 3.8) 57% M	Disease location (isolated SB vs SB + colonic vs isolated colonic)	B2, B3	Median: 2.8 y (range: 1 d to 16.7 y) CI reported at 10 y
Henderson et al (2015)[7]	Retrospective, multicenter	181 CD Median, 11.6 y (range, 9.5–13.1 y) 57% M	Age (0–9 vs 10–16 y) CRP at diagnosis	Surgery	Median: 5.2 y
Herman et al (2017)[51]	Retrospective, single center	209 pediatric CD Median: 14.2 y (IQR 12–16) 58% M	Perianal disease (fistulizing or nonfistulizing)	B2 or B3	Median: 8.5 y (IQR, 5.2–11.7)
Ideström et al (2005)[49]	Retrospective, single center	58 pediatric CD Median: 10.9 y (range, 2.8–16.9 y) 62% M	Genetics (NOD2/CARD15 variant)	B2 Surgery (luminal for stricture/ fistula, not perianal)	Median: 4.2 y (range, 0.9–9.7 y)
Jakobsen et al (2014)[30]	Case control	244 pediatric CD (mixed IBD cohort) Median: 13.4 y (range, 11.6–14.0 y) 54% M	Genetics (NOD2/CARD15 variant)	Surgery	Median: 4.7 y (3–7 y) (entire IBD cohort)
Kugathasan et al (2004)[27]	Prospective, multicenter	163 pediatric CD (138 with CARD15 data) Mean: 12.4 y (range, 3–18 y) 58% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (ileocolonic or ileal resection)	Mean: 39 mo (range, 6–88 mo)
Kugathasan et al (2017)[40]	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 et al (2010)[28]	Prospective, multicenter	171 pediatric CD Mean: 11.8 y (SD, 3.2) 67% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (intestinal resection)	Median: 4.76 y (range, 0.25–13.14 y)
Leonor et al (2007)[9]	Retrospective, single center	280 pediatric CD Median: 11.9 y (IQR: 11.5–12.28) 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 y IQR: 3.02–3.52)

Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Li et al (2013)[45]	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 et al (2015)[42]	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 et al (2015)[50]	Retrospective, single center	65 pediatric CD Mean: 8.6 ± 8.6 y 58% M	Genetics (NOD2/CARD15 variant)	B2 or B3	N/A
Posovszky et al (2013)[29]	Prospective, single center	85 pediatric CD Median (group 1): 22 y (range, 17–35 y) Median (group 2): 20 y (range, 15–26 y) 54% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery	Min: 2 y
Rieder et al (2012)[32]	Prospective, single center	59 pediatric CD Mean: 152 mo (SD, 43) 61% M	$gASCA^{+}$	B2 or B3 (or perianal fistula) Surgery	N/A
Rinawi et al (2016)[44]	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 et al (2016)[16]	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 et al (2005)[26]	Retrospective, multicenter	167 pediatric CD Median: 11.5 y 54% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (any except examination under anesthesia)	2 y

Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Savoye et al (2012)[4]	Retrospective, multicenter	309 pediatric CD Median: 14 y (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 y (range, 7–12 y) Min: 5 y
Schaefer et al (2010)[5]	Prospective, multicenter	498 pediatric CD 5% 0–5 y, 56% 6–12 y, 39% 13–16 y 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 y (95% CI, 1.75–2.25)
Shaoul et al (2009)[18]	Retrospective, single center	128 pediatric CD Mean: 12.8 $\pm$ 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 $\pm$ 3.6 y Min: 2 y
Strisciuglio et al (2014)[23]	Retrospective, single center	74 pediatric CD Median: 11 y (range, 0.7–17.9 y) 66% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery Number of relapses	Min: 1 y
Sun et al (2003)[24]	Retrospective, single center	55 pediatric CD Mean: 11.2 y (range, 1–17.5 y)	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (intestinal resection)	N/A
Sýkora et al (2006)[43]	Prospective, multicenter	46 pediatric CD Mean: 15.3 y (SD, 2.8) 54% M	Age (continuous) Disease location (isolated SB vs SB + colonic vs isolated colonic) Genetics (TNF-α polymorphism)	B2, B3 (internal fistula, inflammatory mass/abscess, perianal fistula) Surgery (luminal resection)	N/A
Tomer et al (2003)[48]	Retrospective, single center	101 pediatric CD Mean: 11.8 y (range, 0.3–18 y) y 66% M	Genetics (NOD2/CARD15 variant)	B2, B3	Mean 49 mo (range, 28 d to 141 mo)

Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Vernier-Massouille et al (2008)[10]	Retrospective, multicenter	404 pediatric CD Median: 14 y (range, 12–16 y) 54% M	Sex, age Disease location (ileal or ileocolonic vs colonic), disease behavior Perianal disease Growth delay (BMI ≤ -2 SD)	Surgery (partial SB resection, partial/total colectomy)	Median: 84 mo (range, 52–124 mo)
Zwintscher et al (2015)[14]	Retrospective (health administrative database), multicenter	7845 pediatric (<20 y) CD, mixed cohort Mean: 15.6 y (SD, 3.9) 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

CI, cumulative incidence; CRP, C-reactive protein; EIM, extraintestinal manifestations; gASCA, anti-glycan ASCA; ICD-9, International Classification of Diseases, Ninth Revision; I/D, incision and drainage; IQR, interquartile range; LB, large bowel; M, male; Min, minimum; N/A, not available; pANCA, perinuclear antineutrophil cytoplasmic antibody; PGA, Physician Global Assessment; SA, South Asian; SB, small bowel; SDS, standard deviation scores; SEM, standard error of the mean.

studies did not report a significantly increased 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 3 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 6 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 2*D*).[22–26,28]

Disease behavior was evaluated as a risk factor for surgery in 4 studies.[5,8,10,16] Pooled HR of 2.55 for B3 disease behavior (95% CI, 0.95–6.88; $P = .06$, n = 1248; $I^2 = 46.0\%$) (Figure 2*E*)[5,10] and a pooled HR of 3.97 (95% CI, 1.56–10.10; $P = .004$; n = 1248; $I^2 = 81.1\%$) (Figure 2*F*) for B2 disease behavior was found.[5,10] Rinawi et al[16] found children with B2/B3 disease to be at increased risk of surgery (aHR, 2.54; 95% CI, 1.59–4.05; $P < .001$).

Five[6,16,17,21,31] out of 8 studies[6,16,17,21,31–34] evaluating the association between ASCA status and surgery showed a significant association. The pooled OR for 5 meta-analyzable studies was 2.31 (95% CI, 1.74–3.06; $P < .0001$; n = 1128; $I^2 = 0$) (Figure 2*G*).[16,17,21,31,32] The pooled HR for 4 of these studies also showed a significantly increased risk of surgery (HR, 2.59; 95% CI, 1.63–4.11; $P < .0001$; n = 1033; $I^2 = 0\%$) (Supplementary Figure 2*C*).[6,16,17,21] Of the 3 studies without a significant association,[32–34] 1 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 Crohn's 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 (94% agreement).

Three studies[18,39,40] found no association between age and progression to B2 disease, none of which could be meta-analyzed because of differing methods (univariate vs multivariable Cox regression) and age definitions. Two[39,40] of 4 studies,[14,18,39,40] including the Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (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 4. No association was reported between age and progression to the combined outcome of B2 or B3 complications in 4 studies.[41–44] Meta-analysis was not possible because of 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).

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

Study	Representative-ness of exposed cohort	Representative-ness of nonexposed 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 et al (2013)[11]	1	1	1	0	0	1	1	1	6
Ammoury and Pfefferkorn (2011)[20]	1	1	1	1	0	1	1	1	7
Amre et al (2006)[17]	1	1	1	1	2	1	1	1	9
Attard et al (2004)[19]	1	1	1	1	0	1	0	1	6
Birimberg-Schwartz et al (2016)[33]	1	1	1	1	1	1	1	1	8
Chhaya et al (2015)[12]	1	1	1	1	2	1	1	1	9
Cucchiara et al (2007)[58]	1	1	0	0	1	1	1	1	6
De Greef et al (2013)[8]	1	1	1	1	0	1	1	1	7
Desir et al (2004)[34]	1	1	1	1	2	1	1	1	9
Dubinsky et al (2006)[47]	1	1	1	1	0	1	1	1	7
Dubinsky et al (2008)[21]	1	1	1	1	0	1	1	1	7
Eidelwein et al (2007)[35]	1	1	1	1	0	1	1	1	7
Fabian et al (2017)[41]	1	1	1	1	2	1	0	1	8
Ferraris et al (2006)[25]	1	1	1	0	0	1	0	1	5

Table 2. Continued

Study	Representative-ness of exposed cohort	Representative-ness of nonexposed 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)
Gupta et al (2006)[6]	1	1	1	1	2	1	1	1	9
Gupta et al (2008)[39]	1	1	1	0	0	1	0	1	5
Gupta et al (2010)[46]	1	1	1	0	0	1	1	1	6
Henderson et al (2015)[7]	1	1	1	1	2	1	1	1	9
Herman et al (2017)[51]	1	1	1	1	0	1	1	1	7
Jakobsen et al (2014)[30]	1	1	1	1	2	1	1	1	9
Ideström et al (2005)[49]	1	1	1	0	0	1	1	1	6
Kugathasan et al (2004)[27]	1	1	1	0	1	1	1	1	7
Kugathasan et al (2017)[40]	1	1	1	1	2	1	1	1	9
Lacher et al (2010)[28]	1	1	1	0	0	1	1	1	7
Leonor et al (2007)[9]	1	1	1	1	1	1	1	0	7
Li et al (2013)[45]	1	1	1	1	0	0	0	1	5
Malmborg et al (2015)[42]	1	1	1	1	2	1	1	1	9
Na et al (2015)[50]	1	1	1	0	0	1	0	1	5
Posovszky et al (2013)[29]	1	1	1	0	0	1	1	1	6

Table 2. Continued

Study	Representative-ness of exposed cohort	Representative-ness of nonexposed 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)
Rieder et al (2012)[32]	1	1	1	0	1	1	0	1	6
Rinawi et al (2016)[44]	1	1	1	1	1	1	1	1	8
Rinawi et al (2016)[16]	1	1	1	1	2	1	1	1	9
Russell et al (2005)[26]	1	1	1	0	2	1	1	1	8
Savoye et al (2012)[4]	1	1	1	1	1	1	1	0	7
Schaefer et al (2010)[5]	1	1	1	1	2	1	1	0	8
Shaoul et al (2009)[18]	1	1	1	0	0	1	1	1	6
Strisciuglio et al (2014)[23]	1	1	1	0	0	1	0	1	5
Sun et al (2003)[24]	1	1	1	0	0	1	0	1	5
Sýkora et al (2006)[43]	1	1	1	0	0	1	0	1	5
Tomer et al (2003)[48]	1	1	1	0	0	1	1	1	6
Vernier-Massouille et al (2008)[10]	1	1	1	1	2	1	1	1	9
Zwintscher et al (2015)[14]	1	1	1	0	1	0	0	1	5

NOTE. Based on the Newcastle-Ottawa Scale. All columns, 0 or 1 stars except comparability (0–2 stars); the last column indicates the total number of stars.

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

Figure 1. Summary of consensus recommendations for the management of inflammatory disease.

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

				Absolute effect		Unadjusted relative effect			Adjusted relative effect		
Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	*P* value	OR (95% CI)[a]	HR (95% CI)	*P* value
Growth impairment as a predictor of surgery											
Gupta et al (2006)[6]	Surgery	Growth impairment (not further defined)	128/956				1.99 (1.18–3.37)	**.01**		2.16 (1.24–3.77)	**.007**
*De Greef et al (2013)[8]	Surgery	Height- and BMI-for-age *z*-score at diagnosis	17/155					NS			
Rinawi et al (2016)[16]	Surgery	Growth impairment (as per Paris classification)	143/482	42/107	101/375		1.6 (1.1–2.3)	**.011**			NS
*Savoye et al (2012)[4]	Surgery (composite outcome)	Growth delay BMI, weight or height < -2 SDS	47/309					**<.05**			
*Zwintscher et al (2015)[14,b]	Surgery	Growth impairment (as per ICD-9)	2113/12,465						1.21 (0.86–1.71)		.279
Disease location as a predictor of surgery											
*Ammoury and Pfefferkorn (2011)[20]	Surgery	Esophageal involvement	9/81					.09			
Amre et al (2006)[17]	Surgery	Colon only vs other	35/139	4/32	31/107			.07			
*Attard et al (2004)[19]	Surgery	Jejunum or proximal ileum	/134	11/23	12/111	3.7		**<.03**			
*De Greef et al (2013)[8]	Surgery	Disease location	17/155					NS			
Gupta et al (2006)[6]	Surgery	L2 (colonic) vs L1 (isolated ileal)	/600	/144	/456		0.56 (0.27–1.16)	.12			
*Leonor et al (2007)[9]	Surgery	Disease location	55/280					NS			
*Henderson et al (2015)[7]	Surgery	Disease location	/465					NS			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
Rinawi et al (2016)[16]	Surgery	Colon only vs other for proportions (2 × 2), L2 vs L1 for HR	143/482	7/58	136/424			**.003**		0.70 (0.51–0.96)	**.03**
Schaefer et al (2010)[5]	Surgery	Transverse colon to rectum vs other	57/854	/674	/180					0.35 (0.19–0.64)	**.0007**
*Savoye et al (2012)[4]	Surgery (composite outcome)	UGI disease	47/309					NS			
*Shaoul et al (2009)[18]	Surgery	(Ileo)colonic disease	38/128					**<.04**			
Vernier-Massouille et al (2008)[10]	Surgery	L2 vs L1	176/353				0.60 (0.33–1.10)	.1			
Sex as a predictor of surgery											
Aloi et al (2013)[11]	Surgery	Male vs female	4/36	3/25	1/11			NS			
Amre et al (2006)[17]	Surgery	Male vs female	35/139	15/72	20/67			NS			
Chhaya et al (2015)[12]	Surgery	Male vs female	/1595				0.90 (0.69–1.17)	.43			
Dubinsky et al (2008)[21]	Surgery	Male vs female	140/796							0.59 (0.38–0.91)	**<.009**
Gupta et al (2006)[6]	Surgery	Male vs female	128/989	63/566	65/423			NS		0.65 (0.46–0.93)	**.02**
Leonor et al (2007)[9]	Surgery	Male vs female	55/280	35/167	20/113			NS			
Rinawi et al (2016)[16]	Surgery	Male vs female	143/482	86/280	57/202		1.05 (0.75–1.47)	.78		0.98 (0.68–1.41)	.92
Schaefer et al (2010)[5]	Surgery	Male vs female	57/854	36/498	21/356			NS			
Vernier-Massouille et al (2008)[10]	Surgery	Male vs female	/394				0.96 (0.71–1.30)	.77			NS
*Zwintscher et al (2015)[14,b]	Surgery	Male vs female	2113/12,465						1.17 (1.06–1.30)		**.001**

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
NOD2/CARD15 polymorphisms as a predictor of surgery											
Cucchiara et al (2007)[58]	Surgery	NOD2/CARD15 variant	50/196	23/75	27/121			NS			
*Dubinsky et al (2008)[21]	Surgery	NOD2/CARD15 variant						NS			
Ferraris et al (2006)[25]	Surgery	NOD2/CARD15 variant	12/134	4/50	8/84	0.83 (0.24–2.90)		1			
*Jakobsen et al (2014)[30]	Surgery	Genetic variants including NOD2/ CARD15 variant	/244					NS			
Kugathasan et al (2004)[27]	Surgery	NOD2/CARD15 variant	/163							7.78 (2.74–22.1)	**<.0005**
Lacher et al (2010)[28]	Surgery	NOD2/CARD15 variant	32/171	21/78	11/93	2.75 (1.23–6.14)		**.017**			
*Posovsky et al (2013)[29]	Surgery	NOD2/CARD15 variant	/85	/37	/48			NS			
Russell et al (2005)[26]	Surgery	NOD2/CARD15 variant	45/167	18/33		4.45 (1.98–10.00)		**.0002**			
*Shaoul et al (2009)[18]	Surgery	NOD2/CARD15 variant	38/128	/48	/77			NS			
Strisciuglio et al (2014)[23]	Surgery	NOD2/CARD 15 variant	10/74	2/16	8/58			.89			
Sun et al (2003)[24]	Surgery	NOD2/CARD15 variant	17/55	13/36	4/19			.26			
Stricturing disease (B2) as a predictor of surgery											
De Greef et al (2013)[8]	Surgery	B2	20/155			6.8 (1.8–25.3)	**0.001**				
Schaefer et al (2010)[5]	Surgery	B2	57/854							6.60 (3.39–12.86)	**<.0001**
Vernier-Massouille et al (2008)[10]	Surgery	B2	176/394	/96						2.54 (1.59–4.05)	**<.01**
Internal penetrating disease (B3) as a predictor of surgery											
Schaefer et al (2010)[5]	Surgery	B3	57/854							3.70 (1.80–7.60)	**.0005**

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
Vernier-Massouille et al (2008)[10]	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 et al (2016)[16]	Surgery	B2 and/or B3	143/482	51/115	92/367	2.38 (1.54–3.69)				2.44 (1.69–3.53)	**<.001**
Antimicrobial serologies as a predictor of surgery											
Amre et al (2006)[17]	Surgery	ASCA$^+$ (IgA or IgG)	35/139	24/75	11/64			.05		1.80 (0.84–3.85)	**<.05**
*Birimberg-Schwartz et al (2016)[33]	Surgery	pANCA$^-$/ASCA$^+$	6/146					.326			
*Desir et al (2004)[34]	Surgery	ASCA IgG	/154			2.34 (0.29–18.5)					
Dubinsky et al (2008)[21]	Surgery	ASCA$^+$	61/563			2.2 (1.5–3.2)		**.0001**		3.2 (1.1–9.5)	**<.04**
Gupta et al (2006)[6]	Surgery	ASCA$^+$	/161	7/63	/98		3.43 (1.00–11.76	.05			
Rieder et al (2012)[32]	Surgery	gASCA$^+$	20/59		/22				1.4 (0.4–5.0)[b] 1.9 (0.55–6.4)[c] 2.5 (0.64–9.4)[d]		.59 .32 .19
Rinawi et al (2016)[44]	Surgery	ASCA$^+$	94/170	25/32	69/138		3.10 (1.34–7.19)	**.008**			NS
Russell et al (2009)[31]	Surgery	ASCA$^+$	49/197	27/82	22/115	2.11 (1.10–4.06)		**.03**			
Age as a predictor of stricturing (B2) disease											
*Gupta et al (2008)[39]	B2	Age (6–17 vs 0–5 y)	/989	/857	/83		2.15 (0.99–4.69)	.05			
*Kugathasan et al (2017)[40]	B2	Age (continuous)	54/913							1.07 (0.97–1.17)	.16
*Shaoul et al (2009)[18]	B2	Age (<10, 10–12, >12 y)	20/128					NS			
Race as a predictor of stricturing (B2) disease											
*Kugathasan et al (2017)[40]	B2	Black vs other	54/913	9/121	45/792			.45		1.08 (0.52–2.22)	.84

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
Disease location as a predictor of stricturing (B2) disease											
*Aloi et al (2013)[11]	B2	Disease location	/36					NS			
Gupta et al (2010)[46]	B2	Ileal or ileocolonic vs colon only	/600	103/456	16/144		Cumulative incidence 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)	**.02**			
Kugathasan et al (2017)[40]	B2	Ileal or ileocolonic vs colon only for proportions; isolated ileal vs other for HR	54/913	44/690	10/223			.30		1.60 (0.88–2.91)	.12
Antimicrobial serologies as a predictor of stricturing (B2) disease											
*Aloi et al (2013)[11]	B2	ASCA$^+$ (IgA or IgG)	/36					NS			
*Kugathasan et al (2017)[40]	B2	ASCA IgA$^+$	54/913	22/218	32/695			**.003**		1.69 (0.94–3.07)	.0816
*Kugathasan et al (2017)[40]	B2	CBir1$^+$	54/913	32/341	22/572			**<.001**		2.30 (1.26–4.20)	**.007**
NOD2/CARD15 polymorphisms as a predictor of stricturing (B2) disease											
Ferraris et al (2006)[25]	B2	NOD2/CARD15 variant	22/134	8/50	14/84	1.03 (0.39–2.69)		.95			
*Ideström et al (2005)[49]	B2	NOD2/CARD15 variant	7/58	/5	/53			NS			
Kugathasan et al (2004)[27]	B2	NOD2/CARD15 variant	25/138	20/58	5/80			**.0001**	7.9 (2.94–25.21)[d]		**.0001**
*Kugathasan et al (2017)[40]	B2	NOD2/CARD15 variant	54/913					.14			
Lacher et al (2010)[28]	B2	NOD2/CARD15 variant	29/171	23/78	6/93	6.06 (2.32–15.83)		**<.0001**			
*Na et al (2015)[50]	B2	NOD2/CARD15 variant						NS			
Posovszky et al (2013)[29]	B2	NOD2/CARD15 variant	21/85	15/37	6/48			**.005**			
Russell et al (2005)[26]	B2	NOD2/CARD15 variant	7/167	3/33	4/134			.14			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
Shaoul et al (2009)[18]	B2	NOD2/CARD15 (multiple alleles or heterozygote, any variant)	20/125	8/48	12/77			.87			
Strisciuglio et al (2014)[23]	B2	NOD2/CARD15 variant	8/74	5/16	3/58			**.01**			
Sun et al (2003)[24]	B2	NOD2/CARD15 variant	24/55	18/36	6/19	2.17 (0.67–6.96)		.4			
Tomer et al (2003)[48]	B2	NOD2/CARD15 variant	2/101	1/29	1/72			**.5**			
Age as a predictor of internal penetrating (B3) disease											
*Gupta et al (2008)[39]	B3 (fistula)	Age (6–17 vs 0–5 y)	/989	/857	/83		2.67 (1.15–6.15)	**.02**			
*Gupta et al (2008)[39]	B3 (abscess)	Age (6–17 vs 0–5 y)	/989	/857	/83		7.66 (2.36–24.9)	**.001**			
*Kugathasan et al (2017)[40]	B3	Age (continuous)	24/913							1.45 (1.17–1.80)	**.0008**
*Shaoul et al (2009)[18]	B3	Age (<10, 10–12, >12)	8/128					NS			
*Zwintscher et al (2015)[14]	B3 (complex fistula)	Age (0–5 vs 6–10 vs 11–15 vs 16–20 y)	98/7845								.994
*Zwintscher et al (2015)[14]	B3 (entero-enteral fistula)	Age (0–5 vs 6–10 vs 11–15 vs 16–20 y)	293/ 7845								.994
Race as a predictor of internal penetrating (B3) disease											
Kugathasan et al (2017)[40]	B3	Black vs White	24/913	9/121	15/792			**.001**		3.19 (1.39–7.31)	**.0061**
Li et al (2013)[45]	B3	SA vs White	15/107	3/13	12/94		Cumulative incidence: 15.4 (4.1–4.8) vs 4.4 (1.7–11.4)	**.02**			
Disease location as a predictor of internal penetrating (B3) disease											
*Gupta et al (2010)[46]	B3	Ileal or ileocolonic vs colon only	/600	/456	/144			0.13			

Table 3. Continued

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)[a]	HR (95% CI)	*P* value
*Kugathasan et al (2017)[40]	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)	.64
Antimicrobial serologies as a predictor of internal penetrating (B3) disease											
Amre et al (2006)[17]	B3	ASCA IgA$^+$	31/139	23/67	8/72			**.002**		2.84 (1.20–6.72)	**<.05**
*Desir et al (2004)[34]	B3	ASCA IgA$^+$	13/61						0.51 (0.08–3.08)		NS
Kugathasan et al (2017)[40]	B3	ASCA IgA$^+$	24/913	14/218	10/695			**.0002**		2.68 (1.19–6.04)	**.0171**
*Amre et al (2006)[17]	B3	ASCA IgA titer	31/139							1.20 (1.08–1.34)	**<.005**
*Desir et al (2004)[34]	B3	ASCA IgA titer	13/61						1.04 (0.29–3.76)		NS
Amre et al (2006)[17]	B3	ASCA IgG$^+$	31/139	17/59	14/80			.12		2.38 (1.09–5.17)	**<.05**
Desir et al (2004)[34]	B3	ASCA IgG$^+$	13/61						0.72 (0.14–4.22)		NS
*Amre et al (2006)[17]	B3	ASCA IgG titer	31/139							1.12 (0.99–1.28)	NS
*Desir et al (2004)[34]	B3	ASCA IgG titer	13/61						0.91 (0.29–2.75)		NS
*Amre et al (2006)[17]	B3	ASCA IgA$^+$ or IgG$^+$	31/139	23/75	8/64			**.01**		2.33 (0.99–5.50)	NS
*Kugathasan et al (2017)[40]	B3	CBir1$^+$	24/913	16/341	8/572			**.005**		3.01 (1.31–6.93)	**.0097**
Perianal disease as a predictor of internal penetrating (B3) disease											
*Zwintscher et al (2015)[14]	B3 (complex fistula)	Perianal disease (abscess, fissure, fistula)	98/7845						3.50 (1.98–6.20)		**<.001**

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
*Zwintscher et al (2015)[14]	B3 (entero-enteral fistula)	Perianal disease (abscess, fissure, fistula)	293/7845						0.30 (0.15–0.63)		**.001**
NOD2/CARD15 polymorphisms as a predictor of internal penetrating (B3) disease											
Ferraris et al (2006)[25]	B3	NOD2/CARD15 variant	14/134	7/50	7/84	1.8 (0.58–5.55)		.3			
Kugathasan et al (2004)[27]	B3	NOD2/CARD15 variant	24/138	8/58	16/80			.34	0.64 (0.24–1.58)[d]		.345
*Kugathasan et al (2017)[40]	B3	NOD2/CARD15 variant	54/913					.39			
Lacher et al (2010)[28]	B3	NOD2/CARD15 variant	2/171	2/78	0/93			.24			
*Na et al (2015)[50]	B3	NOD2/CARD15 variant						NS			
Posovszky et al (2013)[29]	B3	NOD2/CARD15 variant	21/85	6/37	3/48			.16			
Russell et al (2005)[26]	B3	NOD2/CARD15 variant	24/167	7/33	17/134			.22			
Shaoul et al (2009)[18]	B3	NOD2/CARD15 (multiple alleles or heterozygote, any variant)	8/125	5/48	3/77			.16			
Strisciuglio et al (2014)[23]	B3	NOD2/CARD15 variant	4/74	4/16	0/58			**.01**			
Sun et al (2003)[24]	B3	NOD2/CARD15 variant	12/55	7/36	5/19	0.68 (0.18–2.51)		.82			
Tomer et al (2003)[48]	B3	NOD2/CARD15 variant	19/101	3/29	16/72			.18			
Age as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
*Fabian et al (2017)[41]	B2 or B3 (or perianal fistula or anti-TNF)	Age (continuous)	19/63						RR 0.95 (0.85–1.05)		.29
*Malmborg et al (2015)[42]	B2 or B3 (or anti-TNF use)	Age (>10 vs <10 y)	/161	/51	/110		1.81 (0.83–3.99)	.14		1.00 (0.35–2.85)	.99
*Rinawi et al (2016)[44]	B2 or B3	Age (continuous)	80/174				1.02	.47			NS

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/exposed	Absolute effect: Events/unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
*Sýkora et al (2006)[43]	B2 or B3 (or perianal fistula)	Age	16/46					NS			
Race as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
*Eidelwein et al (2007)[35]	B2 or B3	Race (Black vs White)	21/137	10/34	11/103			**.01**			
Disease location as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Gupta et al (2010)[46]	B2 or B3	Ileal or ileocolonic vs colon only	/600	207/456	32/144		Cumulative incidence 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)	**.0009**			
*Malmborg et al (2015)[42]	B2 or B3 (or anti-TNF use)	Ileal or ileocolonic vs colon only	/161	/130	/31		1.38 (0.63–3.03)	.44			
Rinawi et al (2016)[44]	B2 or B3	Ileal or ileocolonic vs other for proportions; isolated ileal vs other for HR	80/173	63/127	17/46		1	.52			
Sýkora et al (2006)[43]	B2 or B3 (or perianal fistula)	Isolated SB or SB + colonic vs colon only	16/46	14/41	2/5			.80			
Antimicrobial serologies as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Dubinsky et al (2006)[47]	B2 or B3	Seropositive (ASCA, OmpC, I^2, and/or CBir1$^+$)	10/167	8/97	2/70			**.03** (log rank)			
Dubinsky et al (2008)[21]	B2 or B3	Seropositive (ASCA, OmpC, and/or CBir1$^+$)	37/536	32/363	5/173			**.01**			
*Dubinsky et al (2008)[21]	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 **.005** **<.005**			

Table 3. Continued

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect: Events/ exposed	Absolute effect: Events/ unexposed	Unadjusted relative effect: OR (95% CI)	Unadjusted relative effect: HR (95% CI)	Unadjusted relative effect: *P* value	Adjusted relative effect: OR (95% CI)[a]	Adjusted relative effect: HR (95% CI)	Adjusted relative effect: *P* value
*Dubinsky et al (2008)[21]	B2 or B3	ASCA$^+$	37/536					NS			
*Dubinsky et al (2008)[21]	B2 or B3	OmpC$^+$	37/536				2.4 (1.2–4.9)	**.01**			
*Dubinsky et al (2008)[21]	B2 or B3	CBir1$^+$	37/536				2.5 (1.2–5.2)	**<.02**			
*Rieder et al (2012)[32]	B2 or B3 (or perianal fistula)	gASCA$^+$	/59	/37	/22				7.4 (1.4–38.2)[b] 3.9 (1.08–13.8)[c] 2.5 (0.68–9.0)[d]	**.016** **.038** .17	
Perianal disease as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Herman et al (2017)[51]	B2 or B3	Perianal disease (fistulizing or nonfistulizing)	29/209	18/71	11/138			**.001**			
Rinawi et al (2016)[44]	B2 or B3	Perianal disease (tags/fissures)	80/174	10/22	70/152		0.97	.92			

NOTE. An asterisk before the study denotes specific predictor-outcome pairs that could not be meta-analyzed because of heterogeneity or insufficient data, including lack of CD-specific data. *P* values in **bold** indicate significance.
gASCA, anti-glycan ASCA; ICD-9, International Classification of Diseases, Ninth Revision; NS, not significant; pANCA, perinuclear antineutrophil cytoplasmic antibody; RR, relative risk; SA, South Asian; SB, small bowel; SDS, standard deviation score; UGI, upper gastrointestinal.
[a]Unless otherwise stated to be RR.
[b]Adjusted for disease location.
[c]Adjusted for disease duration.
[d]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) • $\geq$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

Table 4. Continued

Outcomes	Predictors	Possible predictors	No association
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		

EIM, extraintestinal manifestations; N/A, not available.

When pooled, 2 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 = 1020; $I^2 = 0\%$) (Figure 3*A*).[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[45] 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 = 1513; $I^2 = 6\%$) (Figure 3*B*). 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; 3 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 3*C*). 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 2 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

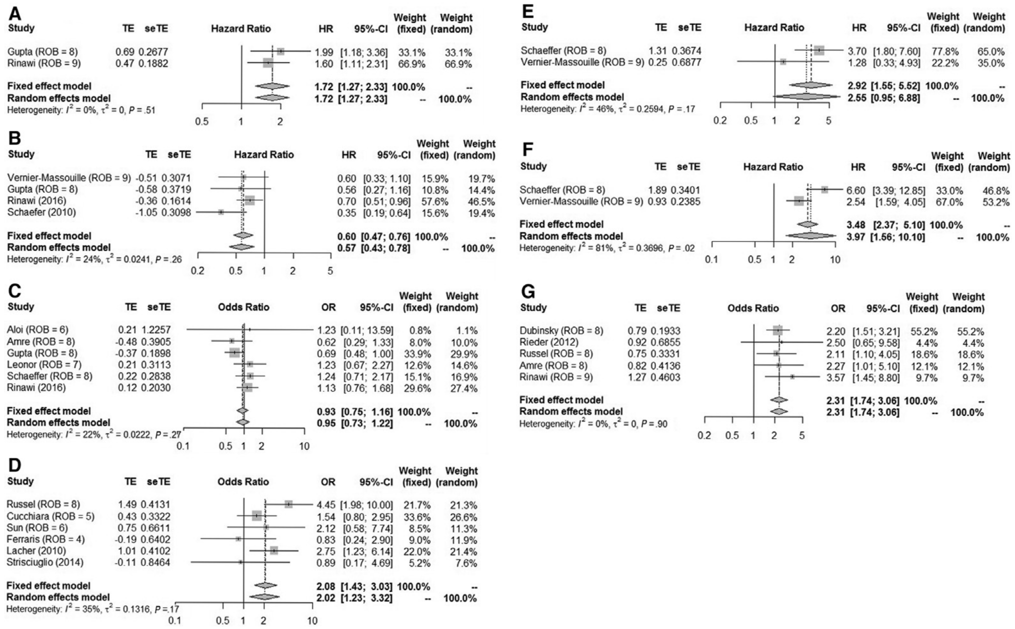

Figure 2. Forest plots for predictors of surgery in pediatric CD: (*A*) poor growth, (*B*) isolated colonic disease, (*C*) male sex, (*D*) NOD2/CARD15 variant, (*E*) B3 behavior, (*F*) B2 behavior, and (*G*) ASCA positivity. ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

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 = 1052; $I^2 = 0\%$) (Figure 3*D*).[17,40] The pooled unadjusted OR for these 2 studies was 4.45 (95% CI, 2.43–8.16; $P < .0001$; $I^2 = 0\%$) (Supplementary Figure 2*D*). A large adjusted study also showed an association between ASCA-IgA titer and B3 disease (HR, 1.20; 95% CI, 1.08–1.34; $P = .0009$; n = 139).[17] The 1 study that did not support an association between ASCA-IgA (positivity or titer) and B3 disease was substantially smaller and did not use survival analysis.[34] On the other hand, for ASCA-IgG positivity, 2 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 3*E*).[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 2 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 3*F*).[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 9 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 = 1050; $I^2 = 55\%$) (Figure 3*G*).[18,23–29,48] The 3 studies that could not be pooled found no association.[40,49,50] Because most of these studies did not adjust for disease location, it is unclear whether the association of *NOD2* with B2 disease stems directly from its association with ileal location. A meta-analysis of 9 of the 11 studies that assessed the association between *NOD2* and B3 complications showed no increased risk (pooled OR, 1.48; 95% CI, 0.78–2.81; $P = .23$; n = 1050; $I^2 = 48\%$) (Figure 3*H*).[18,23–29,48] The 2 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 3*I*). Notably, there was substantial heterogeneity in this analysis. An administrative database study reported an increased risk of internal fistulae (rectourethral,

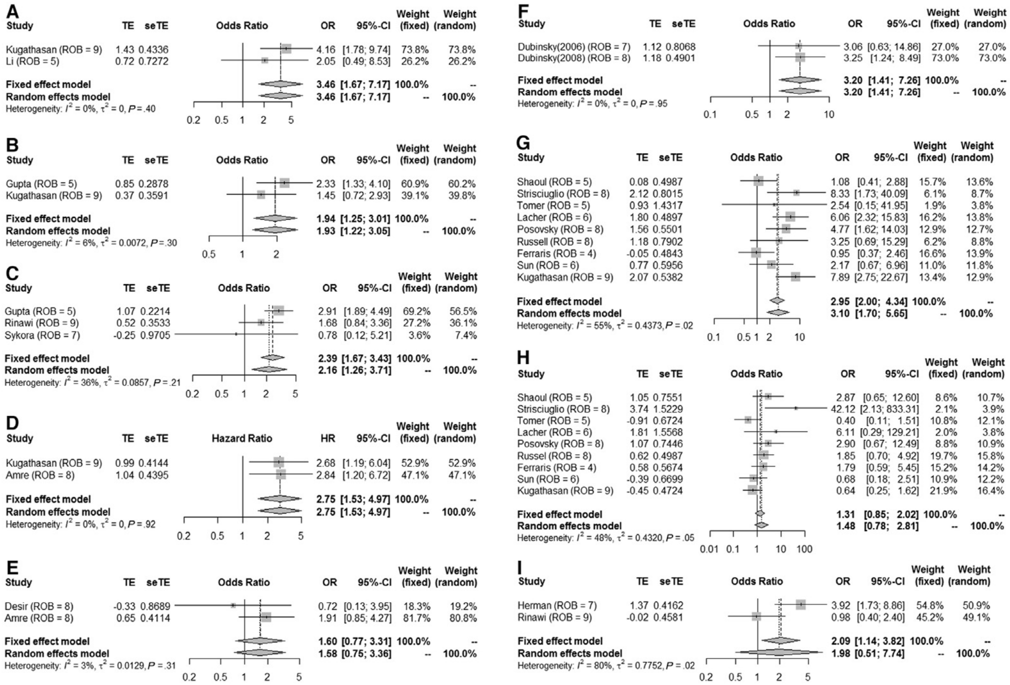

Figure 3. Forest plots for predictors of B2/B3 complications in pediatric CD: (*A*) non-White ethnicity/race as a predictor of B3 complications, (*B*) small bowel disease (± colonic) as a predictor of B2 complications, (*C*) small bowel disease (± colonic) as a predictor of B2 or B3 complications, (*D*) 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, and (*I*) perianal disease as a predictor of B2 or B3 complications.

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 7 of 8 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 (1 study positive,[43] 5 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 7076 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[39] observed a trend toward more perianal disease in children >5 years of age (vs younger children). 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 White 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 1 study.[32] In the RISK cohort, children with perianal disease at diagnosis were more likely to be ASCA IgA/IgG, CBir1, granulocyte-macrophage colony-stimulating factor, 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 1[55] of 3[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, and the other was cross-sectional in nature.[53]

Overall, genetics (2 studies positive[56,57] and 9 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 5 studies found no association between sex and growth,[4,62–65] 4 other large and well-designed studies did observe male patients to be at higher risk of linear growth impairment.[53,66–68] The studies on age in relation to growth impairment are conflicting. Four found no association,[39,53,63,68] although 2 were mixed IBD studies.[63,68] In 4 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 and 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 5 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, although most were cross-sectional rather than truly predictive. Specifically, 2 studies observed an association between more severe clinical disease and impaired growth,[63,70] whereas 2 did not.[8,62] Four studies found an association between higher erythrocyte sedimentation rate and growth impairment,[68,69,72,73] whereas 3 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 1 of which was positive, reporting that 50% of children with at least 1 *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 of 9 studies were positive,[29,79–85,87] and for height, 5 of 8 studies were positive,[79,80,83,85,88] whereas 3 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 because several were cross-sectional.[29,79,81–83,85,87,89–91] Five studies found an association between clinical disease activity and BMD,[29,81,82,85,89] whereas 5 other studies did not,[79,83,87,90,91] including 2 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 7 pediatric studies,[29,53,79,80,83,85,92] whereas 2 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 Crohn's Disease

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] 2 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 1 (n = 240) reported an association with the need for immunomodulators by 1 year.[96] One of 2 studies found an association between B3 behavior and use of anti-TNF.[57,95]

Only 2 of 10 studies reported an association between age and intensified treatment.[3,11,13,39,64,97–101] The first, a prospective registry of 1928 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 4 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 patients with CD from those with UC, 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 3 studies investigating predictive factors of disease severity in pediatric CD,[8,60,65] 2 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 6[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 of >1.0 (vs <1.0).[102] Gasparetto et al[13] found children aged 5–10 years at diagnosis to relapse more frequently than children with disease onset at 11–16 years of age (mean ± standard deviation relapse per patient per year, 1.4 ± 0.2 vs 0.85 ± 0.1, respectively; OR, 1.2; 95% CI, 1.01–1.65). However, because of 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 7 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[103] 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. 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 affect 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 because 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–TNF-α 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. First, 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 the heterogeneity of the included studies. Sources of heterogeneity included definitions of predictors and outcomes, with growth being 1 example of a factor for which various definitions were used, as well as differences in the types of effect measures reported by individual studies. Although 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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.07.065.

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Supplementary 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))

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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]

Supplementary 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 (aHR, 1.12 per 1-year increase in age; 95% CI, 1.06–1.18; $P <$ .0001). The children were divided into 4 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: 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 7 studies. In a study of 506 children with IBD, risk for surgery was equal across 3 groups (0–5 years, 6–11 years, and 12–18 years).[4] A UK retrospective study of patients with IBD (1595 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 patients with CD 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 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 of ≤2 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 PIBD 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 patients with CD 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 2113 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 5 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 1 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 2568 patients with CD of age <17 years, found that, although 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, entero-enteral 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 4 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) were 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 5 studies in children with CD.[1,11,32–34]

Prognostic Risk Factors for Complications in Pediatric Crohn's 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 (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,[30] who found that a higher proportion of Black children progressed to stricturing or penetrating disease than White children (29% of Black children vs 11% of White children; $P = .05$). 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,[44] 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, and 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, and 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.[44] 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 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[25] including 536 children described, 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, because aHRs progressively increased with rising antibody sum scores (aHR of 6 for antibody sum score of 3 vs 0) and increasing quartile sum scores (aHR of 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 1 3020insC allele were 6.6-fold higher (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 1 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 2 studies.[48,50] Of note, it is difficult to estimate accurately the relationship between *NOD2* and B2/B3 complications, because 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 2 studies with inconsistent results.[10,39] A multivariate analysis showed 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 entero-enteral fistulas.[10]

A family history of IBD was not a predictor of complicated disease in multiple studies, including 1 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 (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-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 308G/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, 3 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 2 studies. A retrospective analysis of a prospective observational cohort derived from the ImproveCareNow Network, which included 7076 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[35] 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 serologic markers, including ASCA, anti-laminaribioside carbohydrate antibodies, 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[53] 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). 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 7076 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 of follow-up.[39]

Disease location,[36,39,53] disease behavior,[39] extra-intestinal 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[51] 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 1 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 1 occasion) was significantly associated with younger age. The risk for transient growth failure was almost 7 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 at 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 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 showed an association between higher erythrocyte sedimentation rate and linear growth impairment,[61,65,69] with another showing a positive association between erythrocyte sedimentation rate 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 1456 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, 2 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 3 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 3 studies. Although 2 studies, a retrospective cohort study in children receiving steroid treatment ($n = 221$) and a Belgium registry study, did not report a link,[9,62] 1 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 2 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 more than 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 of $<–1$ 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 the 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 of >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 3 cross-sectional studies, PCDAI was associated with BMD.[78] Furthermore, PCDAI was not found to be associated with BMD in 3 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 3 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 patients with CD (aged 5–25 years).[84]

Prognostic Risk Factors for Chronically Active Inflammatory Pediatric Crohn's Disease. 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 patients with CD, 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[91] 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 ($P = .026$). The other 2 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 with a partial or complete response to therapy.[7,94,95] Additionally, several IBD studies (3 studies with 26, 93, and 993 children with CD and 2 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, 2 studies reported an association, including a prospective observational registry study at multiple centers in North America that included 1928 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 4 studies.[94,96–98] Although 1 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 findings, 2 involved large cohorts with >900 children with CD,[35,96] and 2 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 subanalyses 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, 2 of which identified a link.[9,55,63] A multicenter study with 155 patients with CD 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, because they were identified using 12 SNPs in a study of 65 Korean patients with CD with a mean follow-up of 4.73 years (±4.4 SD), 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 6 studies, there was no strong evidence to support any factors as predictors for relapse because 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 of follow-up in children with a polymorphonuclear neutrophil CD64 index of $>$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 because of 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 7 studies; however, because 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 $\geq$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 $\geq$2 years of follow-up, *NOD2* variants were not predictive of more than 2 weeks of 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 1928 children, no difference was observed in the risk for hospitalization at baseline, 1-year follow-up, or 5-year follow-up among 3 subgroups of children categorized by age at diagnosis (0–5, 6–10, and 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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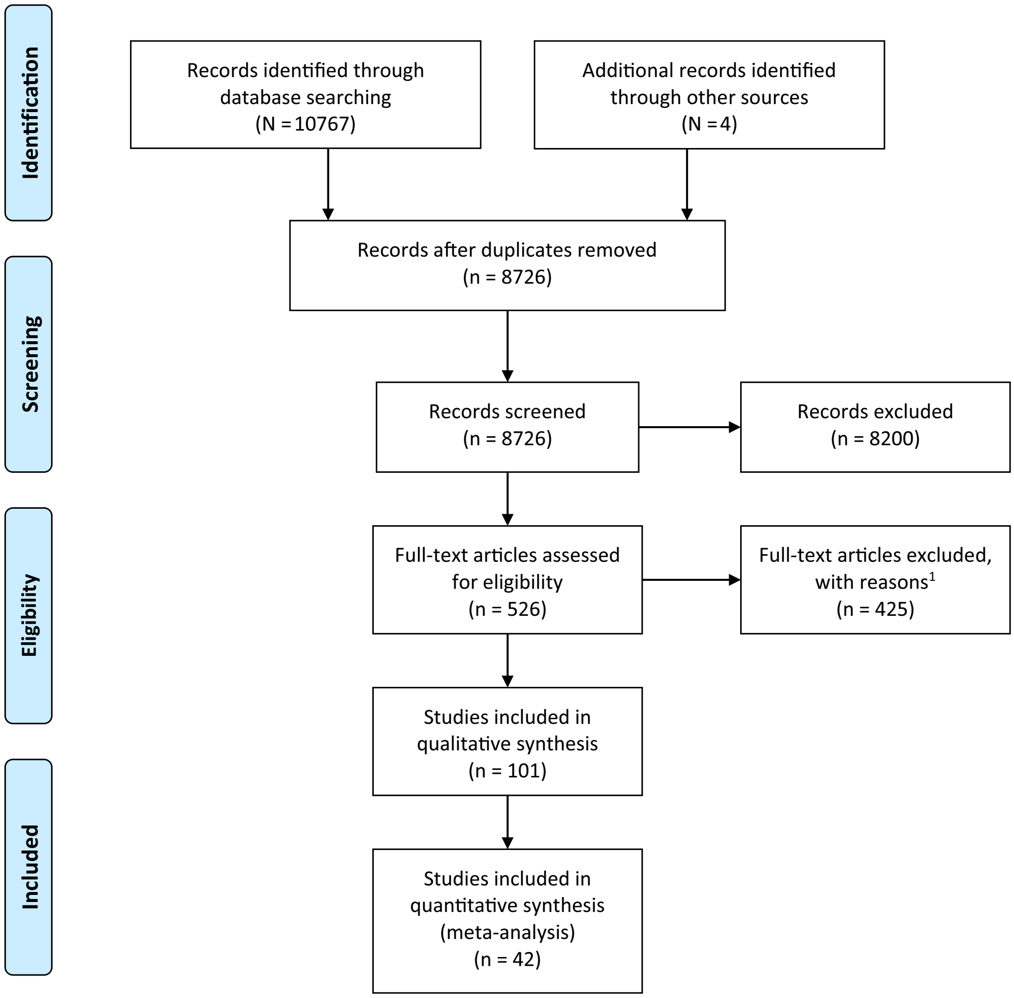
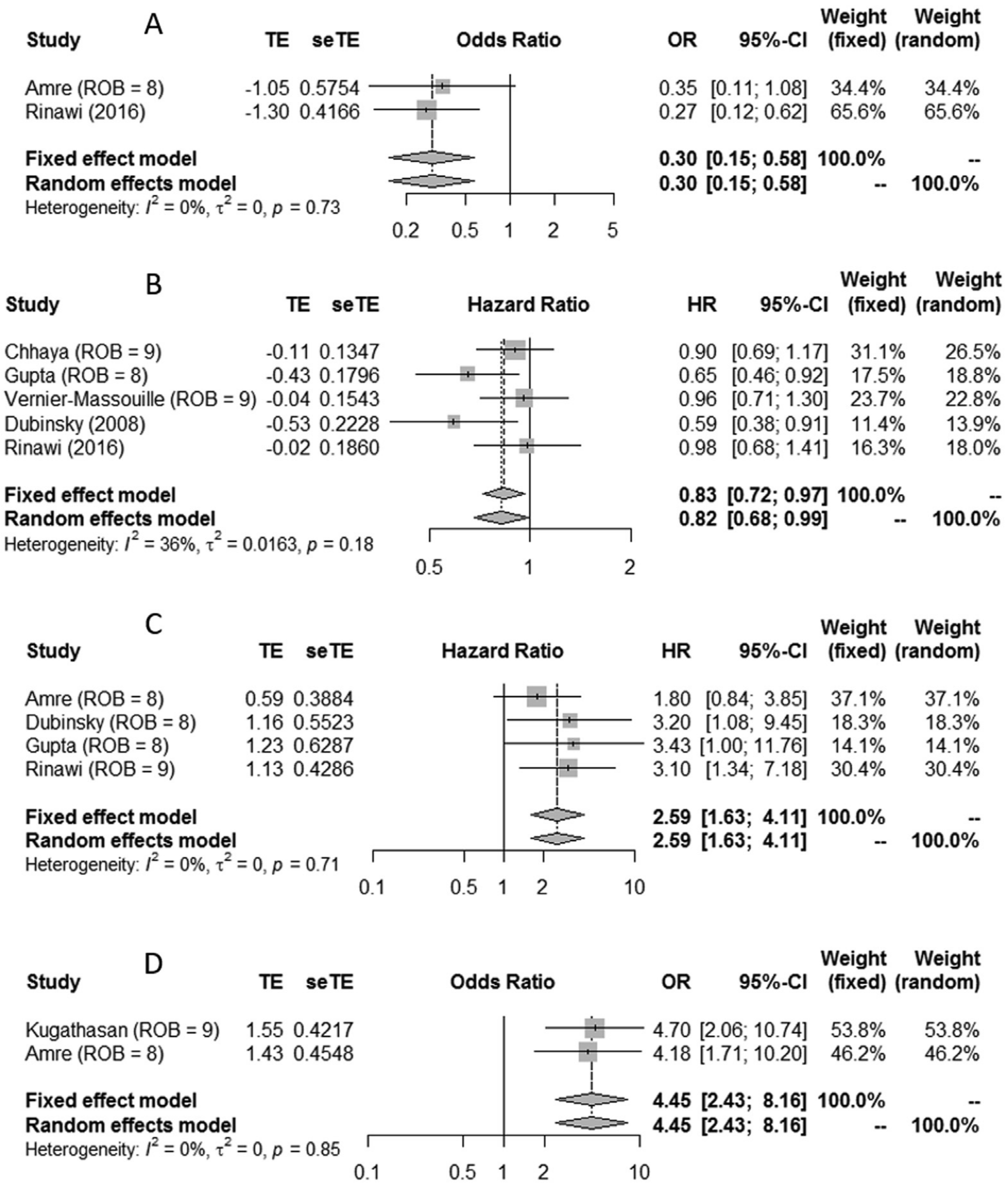


Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.



Supplementary 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, and (*D*) ASCA-IgA positivity as a predictor of B3 complications.

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

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Adler et al (2017)[53]	Prospective,[a] multicenter	6679 pediatric CD Median: 12.4 y (IQR: 9.9–14.8) 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 y (IQR, 0.5–2.6)
Alemzadeh et al (2002)[68]	Retrospective, single center (questionnaire)	135 CD (64 pediatric) 33% M	Disease location, age	Adult height (SDS, height minus target height)	N/A
Aloi et al (2014)[4]	Prospective, multicenter	506 early-onset IBD Mean: 10.2 Y (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 mo (range, 6–50 mo)
Crocco et al (2012)[74]	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 follow-up Immunosuppressive medication	Mean: 3 y (range 2–4 y)
Cucchiara et al (2007)[57]	Retrospective, multicenter	200 pediatric CD Mean: 12 y (SD 4) 49% M	Genetics (TNF variant, MDR1)	Surgery (resection), disease behavior, perianal fistulizing disease, medication use	9 y (SD, 7)
De Matos et al (2008)[32]	Retrospective, single center	184 pediatric CD Median: 12.6 y (range, 1.06–19.7 y) 60% M	Granuloma	Perianal disease (deep fissure, fistula, abscess) Infliximab, surgery (resection, stricturoplasty) B2, B3	Median: 3 y (range, 0.4–8.7 y)
De Ridder et al (2007)[50]	Retrospective, single center	103 pediatric CD Mean: 14 y (range, 6–18 y) 56% M	Genetics (NOD2/CARD15 variants, TLR4, OCTN, DLG5)	B2/B3, surgery, perianal disease	N/A

Supplementary Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Dubner et al (2009)[85]	Retrospective, single center	78 pediatric CD Mean: 12.7 y (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 et al (2016)[62]	Retrospective, single center	221 pediatric CD Mean: 12.4 y (SD, 3.2) 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 y (SD, 2.9)
Freeman (2004)[12]	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)[52]	Prospective, multicenter (database)	114 pediatric CD <17 y 46% M	Granuloma	B2 B3	Mean: >10 y
Gasparetto et al (2016)[8]	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 et al (2010)[101]	Retrospective, single center	67 pediatric CD (mixed IBD cohort)	Growth deficiency	Number of relapses	Mean: 4.8 years
Gupta et al (2004)[87]	Retrospective, single center	123 pediatric CD Mean: 11.8–11.9 y (SD, 2.4–2.9) 53% M	Sex	BMD (increase/loss spine BMD corresponding to highest/lowest quartiles)	Min: 3.4 y
Gupta et al (2007)[51]	Retrospective, multicenter	989 pediatric CD Mean: 11.5 y (SD, 3.8) 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 to 16.7 y)

Supplementary Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Hussey et al (2011)[75]	Retrospective, single center	21 pediatric CD Mean: 15.7 y (SD, 1.98) 71% M	Oral manifestations	Growth (weight and height *z*-scores), relapse	Mean: 55 mo (SD, 22)
Ideström et al (2014)[34]	Retrospective, single center	45 pediatric CD Median: 10.3 60% M	Granuloma	Growth (final adult height SDS adjusted for target height), disease behavior, surgery	Median: 12.3 y (range, 9.3–18 y)
Jakobsen et al (2011)[94]	Retrospective, single center	105 pediatric CD (mixed IBD cohort) Median: 12.8 y (range, 0.4–14.9) y M 54%	Age, sex	Medication use	Median: 4.9 y (IQR, 3.9–7.6)
Jacobstein et al (2006)[92]	Retrospective, single center	57 pediatric CD patients	PCDAI at diagnosis	Medication use	Min: 6 mo
Laakso et al (2014)[77]	Prospective, single center	17 pediatric CD Median: 14.5 y (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 y (range, 4.9–6.3 y)
Latiano et al (2009)[58]	Retrospective, multicenter	265 pediatric CD <19 y 57% M	Genetics (IRGM variant)	Perianal disease, internal fistulizing disease	Mean: 8 y (SD, 7)
Ledder et al (2014)[95]	Retrospective, multicenter	47 pediatric CD (mixed IBD cohort)	Age (<6 vs 6–17 y)	Medication use	Mean: 4.5–4.9 y
Lee et al (2010)[61]	Prospective, multicenter	211 pediatric CD (mixed IBD cohort) Mean: 13.9 y (SD, 3.9) 57% M	Sex, age, diagnostic delay, EIM, family history of IBD, ethnicity Parental height, minimum height *z*-score during follow-up ESR, ethnicity	Growth (final adult height)	Mean: 2.3 y
Lee et al (2012)[96]	Cross-sectional, multicenter	993 pediatric CD Median: 16.6 y (IQR, 14.2–18.6) (M); 16.8 (IQR, 14.4–18.7) (F) 57% M	Sex, age	Growth (BMI *z*-score, height velocity), medication use	Median: 16.6 mo

Supplementary Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Lee et al (2014)[66]	Retrospective single center	54 pediatric CD Mean: 15–16 y (SD, 2–4) 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 et al (2015)[56]	Retrospective, multicenter	108 pediatric CD Mean: 13 y (SD, 2.8) 69% M	Genetics (TNFSF15) Disease behavior	Perianal disease, medication use (TNF-α)	Mean: 2.7 y (SD, 2.2)
Levine et al (2005)[63]	Retrospective, multicenter	87 pediatric CD Mean: 12.1 y (SD, 3.7) 63% M	Genetics (TNF promoter polymorphisms), sex, age, disease location	Growth (weight and height *z*-score nadir; growth retardation, *z*-score of <–1; failure, z-score of <–2) Disease activity/severity (PCDAI, PGA, hospitalization), second-line therapy (need for surgery or infliximab)	Min: 1 y
Lopes et al (2008)[88]	Retrospective, single center	14 pediatric CD (mixed IBD cohort) Mean: 11.8 y (SD, 4.1) 52% M	Age, height-for-age z-score, BMI z-score	BMD (lumbar *z*-score, <–2)	N/A
Malik et al (2012)[65]	Retrospective, single center	116 pediatric CD Mean age: 10.8 y (range 2.9–15.5 y) 59% M	Age, disease activity (biomarker), weight SDS	Growth (height SDS, height velocity SDS)	Mean: 4.6 y
Mason et al (2011)[70]	Retrospective, single center	41 pediatric CD Median: 12.8 y (range, 5.3–14.5 y) (M); 11.6 (range, 8.5–12.8 y) (F) 73% M	Disease activity (biomarker)	Growth (peak height velocity SDS, height SDS)	Min: 2 y
Mason et al (2015)[69]	Prospective, single center	45 pediatric CD Median: 13.4 y (range, 10–16.6 y)	Disease activity (biomarker)	Growth (height and height velocity SDS, change in height SDS)	12 mo
Minar et al (2014)[100]	Retrospective, single center	83 pediatric CD Median: 15 y (range, 1–24 y) 61% M	Neutrophil CD64 index	Clinical relapse	12 mo

Supplementary Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Mossop et al (2008)[97]	Retrospective, single center	93 pediatric CD (mixed IBD cohort)	Sex, age	Medication use (immune modulator)	3.9 y (0.5–10.6)
Müller et al (2016)[91]	Prospective, multicenter	240 pediatric CD (mixed IBD cohort) Median: 14.2 y (IQR, 11.8–16.1 y) 56% M	PCDAI at diagnosis	Medication use (anti–TNF-α)	12 mo
Newby et al (2008)[73]	Retrospective, multicenter	116 pediatric CD (mixed IBD cohort) Median: 11.8 y (range 4–16 y) 72% M	Diagnostic delay Age, sex	Growth (height SDS) Surgery	Mean: 3.4 y (CD)
Olbjorn et al (2014)[93]	Retrospective, multicenter	37 pediatric CD Median: 13 y 56% M	PCDAI at diagnosis B3	Medication use (anti–TNF-α)	Median: 20 mo (range, 12–24 mo)
Olbjorn et al (2017)[90]	Retrospective, multicenter	37 pediatric CD Median: 13.9 57% M	ASCA	Medication use (anti–TNF-α)	Median: 20 mo (range, 12–24 mo)
Oliva-Hemker et al (2015)[99]	Prospective, multicenter	1928 pediatric IBD Median: 12.4 y 56% M	Age (1–5 vs 6–10 vs 11–16 y)	Medication use Hospitalization	Median: 3.25 y
Olives et al (1997)[55]	Retrospective, multicenter	64 pediatric CD (mixed IBD cohort) Mean: 10.9 y (SD, 2.1) (CD) 56% M	ANCA	Disease activity (clinical, endoscopic), perianal disease	N/A
Paganelli et al (2007)[83]	Prospective, single center	35 pediatric CD Mean: 13.5 y (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 et al (2015)[80]	Retrospective, single center	18 pediatric CD Median: 7.8 y (range, 2.9–15.3 y) 28% M	Anthropometrics (BMI, weight, height SDS) Disease activity (PCDAI)	BMD (areal BMD, bone mineral apparent density SDS)	1 y

Supplementary Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Rothschild et al (2017)[33]	Retrospective, single center	289 pediatric CD Median: 14.2 y 68% M	Granulomas	Hospitalization, intestinal resection, B2/B3	Median: 8.5 y
Russell et al (2009)[26]	Retrospective	197 pediatric CD Median: 11.25 y (IQR, 8.75–13) 58% M	ASCA	Surgery	N/A
Samson et al (2010)[79]	Prospective, single center	27 pediatric CD Median: 12.5 y (IQR, 7.2–15.9) 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 chronologic and bone age)	1 y
Sawczenko et al (2006)[59]	Retrospective, multicenter	123 pediatric CD Mean: 12.2 y (SD, 2.8) 53% M	Diagnostic delay, prepubertal status, age, sex, disease location, midparental height *z*-scores	Growth (final height SDS, when growth velocity <1 cm/y $\times$ at least 6 mo)	Mean: 10.4 y (SD, 7.1)
Schmidt et al (2009)[81]	Cross-sectional, multicenter	45 pediatric CD Range: 6–19 y 65% M	Anthropometrics (weight, height, BMI) Age, sex, disease duration	BMD (BMD *z*-score <-2)	2 y
Schmidt et al (2012)[89]	Cross-sectional, multicenter	37 pediatric CD (mixed IBD cohort) Range: 6–19 y 64% M	Sex, age, height (change in *z*-score)	BMD (change)	2 y
Semeao et al (1999)[84]	Retrospective, single center	119 pediatric CD Mean: 16.2 y (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 et al (2016)[86]	Cross-sectional	15 pediatric CD Mean: 13.7 y (SD, 2.6) 62% M	Anthropometrics (weight, height, BMI *z*-score) Disease activity (PCDAI)	BMD (*z*-score)	N/A
Størdal et al (2004)[3]	Prospective, multicenter	16 CD (mixed IBD cohort)	Age	Surgery (for B2 complications)	5 y

Supplementary Table 1. Continued

Study	Study design	Population IBD type, age, and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Sylvester et al (2007)[78]	Prospective, multicenter	48 pediatric CD Mean: 13 y (SD, 3)	Anthropometrics (change in BMI, height) Disease activity (PCDAI), location	BMD (change in *z*-score)	2 y
Sylvester et al (2009)[71]	Prospective, multicenter	42 pediatric CD Mean: 12.6 y (SD, 2.8) 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 et al (2011)[72]	Retrospective, multicenter	1456 pediatric CD <18 y 56% M	Diagnostic delay	Growth failure (as per treating physician)	N/A
Tsampalieros et al (2013)[82]	Prospective, single center	76 pediatric CD Mean: 12.6 y (SD, 2.8) 55% M	Age, sex, disease activity (PCDAI)	BMD (change in trabecular, cortical BMD *z*-score, change in cortical area *z*-score)	Median: 42 mo (range, 23–54 mo) Min: 12 mo
Tung et al (2006)[98]	Retrospective, multicenter	26 pediatric CD (mixed IBD cohort) Median: 15.2 (range, 8.4–18.8) y 62% M	Age, sex	Medication use	12 mo
Uko et al (2014)[103]	Retrospective, single center	101 pediatric CD (mixed IBD cohort) Median: 16 y (range, 14–17) y 55% M	Visceral adipose tissue	Hospitalization Surgery	Min: 12 mo
Vasseur et al (2010)[60]	Retrospective, multicenter	261 pediatric CD Median: 13 y (IQR, 11.2–15.4) 60% M	Age, sex, EIM, upper GIT	Height, weight, BMI	Median: 73 mo (IQR, 46–114) Min: 2 y
Wine et al (2004)[67]	Retrospective, multicenter	93 pediatric CD Mean: 12.1 y (SD, 3.6) 60% M	Genetics (NOD2 variant) Disease activity, location	Weight, height failure (*z*-score <–2)	Min: 1 y
Zwintscher et al (2014)[49]	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

CSA, cross-sectional area; EIM, extraintestinal manifestation; ESR, erythrocyte sedimentation rate; F, female; GIT, gastrointestinal tract; ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; M, male; Min, minimum; N/A, not available; PGA, physician global assessment; sPCDAI, short pediatric Crohn's Disease Activity Index; SB, small bowel; SDS, standard deviation score.
[a]Retrospective analysis of prospectively collected data

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

Study	Representativeness of exposed cohort	Representativeness of nonexposed 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 et al (2017)[53]	1	1	1	1	2	1	1	1	9
Alemzadeh et al (2002)[68]	1	1	0	1	0	0	1	1	5
Aloi et al (2014)[4]	1	1	1	1	0	1	1	1	7
Crocco et al (2012)[74]	1	1	1	1	0	1	1	1	7
Cucchiara et al (2007)[57]	1	1	0	0	0	1	1	1	5
De Matos et al (2008)[32]	1	1	1	1	0	1	1	1	7
De Ridder et al (2007)[50]	1	1	1	0	0	1	0	1	5
Dubner et al (2009)[85]	1	1	1	1	2	1	0	1	8
Duchatellier et al (2016)[62]	1	1	1	1	2	1	1	0	8
Freeman (2004)[12]	1	1	1	0	1	1	1	1	7
Freeman (2007)[52]	0	0	1	0	0	1	1	1	4
Gasparetto et al (2016)[8]	1	1	1	1	2	1	1	1	9
Guariso et al (2010)[101]	1	1	1	1	0	1	1	0	6
Gupta et al (2004)[87]	1	1	1	1	1	1	1	1	8
Gupta et al (2007)[51]	1	1	1	0	1	0	1	1	6

Supplementary Table 2. Continued

Study	Representativeness of exposed cohort	Representativeness of nonexposed 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)
Hussey et al (2011)[75]	1	1	1	0	0	1	1	0	5
Ideström et al (2014)[34]	1	1	1	0	0	1	1	1	6
Jakobsen et al (2011)[94]	1	1	1	1	2	1	1	1	9
Jacobstein (2006)[92]	1	1	1	1	0	1	0	0	5
Laakso et al (2014)[77]	0	0	1	0	1	1	1	1	5
Latiano et al (2009)[58]	1	1	1	0	0	0	1	1	5
Ledder et al (2014)[95]	1	1	1	1	0	1	1	1	8
Lee et al (2010)[61]	0	0	1	0	2	1	1	1	6
Lee et al (2012)[96]	1	1	1	0	1	1	0	1	6
Lee et al (2014)[66]	1	1	1	0	0	1	0	1	5
Lee et al (2015)[56]	1	1	1	0	0	1	1	1	6
Levine et al (2005)[63]	1	1	1	1	2	1	0	1	8
Lopes et al (2008)[88]	0	0	1	0	0	1	0	1	3
Malik et al (2012)[65]	1	1	1	1	0	1	1	1	7
Mason et al (2011)[70]	1	1	1	0	0	1	1	1	6
Mason et al (2015)[69]	1	1	1	0	0	1	0	1	5

Supplementary Table 2. Continued

Study	Representativeness of exposed cohort	Representativeness of nonexposed 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)
Minar et al (2014)[100]	1	1	1	1	1	1	1	1	8
Mossop et al (2008)[97]	1	1	1	1	0	1	1	1	8
Müller et al (2016)[91]	1	1	1	1	1	1	1	1	8
Newby et al (2008)[73]	1	1	1	0	0	1	1	1	6
Oliva-Hemker et al (2015)[99]	1	1	1	1	0	1	1	1	7
Olbjorn et al (2014)[93]	1	1	1	1	0	1	1	1	7
Olbjorn et al (2017)[90]	1	1	1	1	0	1	1	1	7
Olives et al (1997)[55]	1	1	1	0	0	1	0	1	5
Paganelli et al (2007)[83]	1	1	1	1	2	1	0	1	8
Pichler et al (2015)[80]	0	0	1	1	1	1	1	1	6
Rothschild et al (2017)[33]	1	1	1	1	0	1	1	1	7
Russell et al (2009)[26]	1	1	1	1	0	1	0	0	5
Samson et al (2010)[79]	1	1	1	1	1	1	1	0	7
Sawczenko et al (2006)[59]	1	1	1	1	0	1	1	0	6
Schmidt et al (2009)[81]	1	1	1	1	1	1	1	0	7

Supplementary Table 2. Continued

Study	Representativeness of exposed cohort	Representativeness of nonexposed 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)
Schmidt et al (2012)[89]	1	1	1	1	2	1	1	0	8
Semeao et al (1999)[84]	0	1	1	0	2	1	0	1	6
Setty-Shah et al (2016)[86]	0	0	1	0	0	1	0	1	2
Størdal et al (2004)[3]	0	1	1	1	0	1	1	0	5
Sylvester et al (2007)[78]	1	1	1	1	0	1	1	0	6
Sylvester et al (2009)[71]	1	1	1	1	0	1	1	0	6
Timmer et al (2011)[72]	1	1	0	1	0	0	1	1	5
Tsampalieros et al (2013)[82]	0	1	1	1	0	1	1	0	5
Tung et al (2006)[98]	1	1	1	1	0	1	1	0	6
Uko et al (2014)[103]	1	1	1	1	2	1	1	1	9
Vasseur et al (2010)[60]	1	1	1	1	2	1	1	0	8
Wine et al (2004)[67]	1	1	1	1	2	1	1	0	8
Zwintscher et al (2014)[49]	1	1	1	0	2	1	0	1	7

NOTE. Based on the Newcastle-Ottawa Scale. All columns, 0 or 1 stars except comparability (0–2 stars); the last column indicates the total number of stars.