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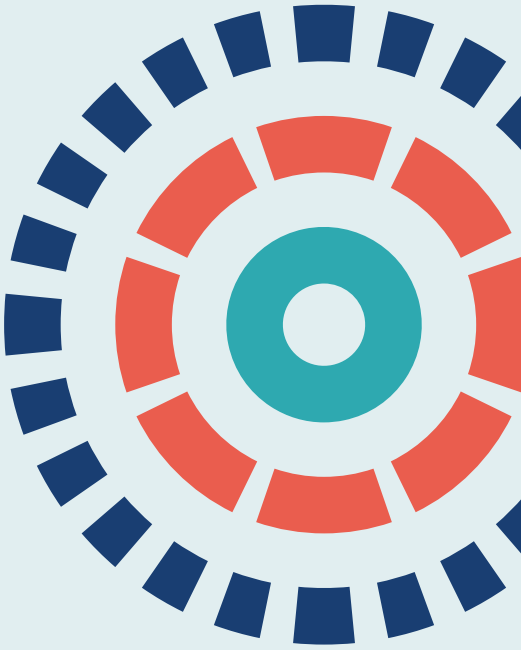

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Prognostic biomarkers to identify patients likely to develop severe Crohn's disease: a systematic review

Steve Halligan,[1*] Darren Boone,[1] Lucinda Archer,[2] Tariq Ahmad,[3] Stuart Bloom,[4] Manuel Rodriguez-Justo,[5] Stuart A Taylor[1] and Sue Mallett[1]

[1]Centre for Medical Imaging, University College London, London, UK
[2]Centre for Prognosis Research, School of Primary, Community and Social Care, Keele University, Keele, UK
[3]Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
[4]Department of Gastroenterology, University College Hospital, London, UK
[5]Department of Histopathology, University College Hospital, London, UK

*Corresponding author

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This report

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Abstract

Prognostic biomarkers to identify patients likely to develop severe Crohn's disease: a systematic review

Steve Halligan,[1*] Darren Boone,[1] Lucinda Archer,[2] Tariq Ahmad,[3] Stuart Bloom,[4] Manuel Rodriguez-Justo,[5] Stuart A Taylor[1] and Sue Mallett[1]

[1]Centre for Medical Imaging, University College London, London, UK
[2]Centre for Prognosis Research, School of Primary, Community and Social Care, Keele University, Keele, UK
[3]Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
[4]Department of Gastroenterology, University College Hospital, London, UK
[5]Department of Histopathology, University College Hospital, London, UK

*Corresponding author s.halligan@ucl.ac.uk

Background: Identification of biomarkers that predict severe Crohn's disease is an urgent unmet research need, but existing research is piecemeal and haphazard.

Objective: To identify biomarkers that are potentially able to predict the development of subsequent severe Crohn's disease.

Design: This was a prognostic systematic review with meta-analysis reserved for those potential predictors with sufficient existing research (defined as five or more primary studies).

Data sources: PubMed and EMBASE searched from inception to 1 January 2016, updated to 1 January 2018.

Review methods: Eligible studies were studies that compared biomarkers in patients who did or did not subsequently develop severe Crohn's disease. We excluded biomarkers that had insufficient research evidence. A clinician and two statisticians independently extracted data relating to predictors, severe disease definitions, event numbers and outcomes, including odds/hazard ratios. We assessed risk of bias. We searched for associations with subsequent severe disease rather than precise estimates of strength. A random-effects meta-analysis was performed separately for odds ratios.

Results: In total, 29,950 abstracts yielded just 71 individual studies, reporting 56 non-overlapping cohorts. Five clinical biomarkers (Montreal behaviour, age, disease duration, disease location and smoking), two serological biomarkers (anti-*Saccharomyces cerevisiae* antibodies and anti-flagellin antibodies) and one genetic biomarker (nucleotide-binding oligomerisation domain-containing protein 2) displayed statistically significant prognostic potential. Overall, the strongest association with subsequent severe disease was identified for Montreal B2 and B3 categories (odds ratio 4.09 and 6.25, respectively).

Limitations: Definitions of severe disease varied widely, and some studies confounded diagnosis and prognosis. Risk of bias was rated as 'high' in 92% of studies overall. Some biomarkers that are used regularly in daily practice, for example C-reactive protein, were studied too infrequently for meta-analysis.

Conclusions: Research for individual biomarkers to predict severe Crohn's disease is scant, heterogeneous and at a high risk of bias. Despite a large amount of potential research, we encountered

relatively few biomarkers with data sufficient for meta-analysis, identifying only eight biomarkers with potential predictive capability.

Future work: We will use existing data sets to develop and then validate a predictive model based on the potential predictors identified by this systematic review. Contingent on the outcome of that research, a prospective external validation may prove clinically desirable.

Study registration: This study is registered as PROSPERO CRD42016029363.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 45. See the NIHR Journals Library website for further project information.

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List of abbreviations

anti-CBir1	anti-flagellin antibody
anti-TNF	anti-tumour necrosis factor
ASCA	anti-*Saccharomyces cerevisiae* antibodies
CDAI	Crohn's Disease Activity Index
CHARMS	CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
CI	confidence interval
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
HTA	Health Technology Assessment
IBD	inflammatory bowel disease
Ig	immunoglobulin
IQR	interquartile range
JAK	Janus kinase
MeSH	medical subject heading
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NOD2	nucleotide-binding oligomerisation domain-containing protein 2
OR	odds ratio
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBAST	Prediction model Risk Of Bias Assessment Tool
ROB	risk of bias
STAT	signal transducer and activator of transcription
TA	Technology Appraisal
TNF	tumour necrosis factor
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
WBC	white blood cell

Plain English summary

Crohn's disease causes inflammation of the intestines. Traditional treatment uses drugs, such as steroids, at a gradually increasing dose as symptoms worsen. Newer 'biological' drugs may stop disease, but are not used as an early treatment because they are expensive and have serious side effects. Using biologicals early means knowing which patients will develop severe disease in the future.

A 'prognostic biomarker' is a measurement made on a patient that predicts a future outcome. A lot of research has attempted to identify biomarkers that predict severe Crohn's disease, but research is haphazard and of variable quality. We therefore carried out a 'systematic review', which identifies research in a comprehensive and unbiased fashion. We found nearly 30,000 research papers, 71 of which were acceptable quality and described 56 groups of Crohn's disease patients. We then used a statistical method called 'meta-analysis' to combine results from multiple studies. This allowed us to identify the most promising biomarkers to predict future severe disease. We found five clinical biomarkers (e.g. age and smoking), two blood biomarkers and one genetic biomarker that seemed reasonably able to predict future severe Crohn's disease.

However, we also found that most research was poorly performed and frequently confused diagnosis (current disease) with prognosis (future disease). Some commonly used biomarkers were not sufficiently investigated. We were surprised to identify so few prognostic biomarkers in the face of a seemingly vast amount of research.

Future research should be better conducted and not confuse diagnosis with prognosis. We will use statistical methods to combine the promising biomarkers that we identified into a 'prognostic model', which is a mathematical formula that provides the likelihood of developing severe disease in the future. We will then test how well this works by using patient data from existing Crohn's disease databases.

Scientific summary

Background and objectives

The research detailed in this monograph arose from the National Institute for Health Research Health Technology Assessment programme call HTA 14/210: 'Prognostic markers in early Crohn's disease'. The need for this research turns on the understanding that early administration of biological therapies to patients with Crohn's disease may prevent disease progression. Indiscriminate administration of biologicals to all patients with a new diagnosis of Crohn's disease would not, however, be sensible because these drugs are both expensive and associated with serious side effects in a small but significant number of patients. Administering biologicals to patients whose disease is destined to be indolent would necessitate extensive over-treatment. Therefore, the unmet need is for a tool that accurately predicts those patients with a new diagnosis of Crohn's disease whose disease is destined to become severe at some point in the future. Biological therapy could be targeted to this group of patients and over-treatment avoided elsewhere. This approach would also probably be cost-effective.

A 'prognostic biomarker' is a measurement made on a patient that predicts a future event, for example a biological process and/or health state. Biomarkers may also be 'diagnostic', that is their level represents a current health state, for example the presence or absence of active disease. Some biomarkers may be both diagnostic and prognostic. The primary objective of this research was to perform a comprehensive systematic review across all biomarker types used for Crohn's disease (e.g. clinical, serological, genetic, radiological, endoscopic and histological), with the aim of identifying those that display potential prognostic capability for prediction of subsequent severe disease.

Review methods

The review was registered (PROSPERO CRD42016029363) and the protocol published. Following a scoping search, a clinical researcher experienced in systematic review and multidisciplinary Crohn's disease management designed and performed the search, supervised by co-researchers, including statisticians with extensive prior experience of prognostic systematic reviews, methodology experts and disease experts. Using an inclusive strategy, our search string combined five clusters of terms to identify (1) Crohn's disease, (2) severe disease, (3) biomarkers, (4) terms to identify prediction/prognosis and (5) exclusion criteria (e.g. animal research and narrative reviews). Hand-searching was also adopted. The PubMed and EMBASE databases were searched from inception to 1 January 2016, with an update carried out up to 1 January 2018 for serological biomarkers. The target condition was human Crohn's disease, confirmed by standard criteria. There was no age restriction, with paediatric subgroups identified where possible, and no language restriction. We anticipated finding a plethora of potential biomarkers and set a priori quality/quantity thresholds to prevent including biomarkers with insufficient primary evidence for sensible meta-analysis, stipulating that predictors should be reported in at least five individual studies. We excepted new but exceptionally promising predictors, which were chosen by an expert panel from a list of all candidates identified by the review. The panel also indicated predictors that were already widely used. Given that no generally accepted definition of 'severe' disease exists, we used a broad range of criteria to avoid discarding potentially valuable research. We stipulated a minimum 3-month duration between biomarker measurement and outcome to ensure that the data were prognostic rather than diagnostic.

Full-text articles were examined by Darren Boone and queries were raised with other collaborators. Ultimately, Sue Mallett examined all full-text articles selected for the review and verified data extraction. Data were extracted into a data sheet that included author, journal, design (e.g. cohort,

randomised controlled trial and retrospective database), methods, setting/context (organisation/service type and country), participants (including age range and gender), time since diagnosis (symptom duration and/or time since diagnosis for established disease), markers of severe disease, symptom severity, disease location and burden, disease complications, Crohn's activity indices, surgical details, perianal disease and continence outcomes. In addition, we extracted data specific to the prognostic marker investigated, including measurement (methods, frequency), adverse events, reliability and reproducibility, and costs, where available. We recorded study interventions and outcomes (including definitions, thresholds for severity/remission and whether or not these thresholds were prespecified in the publication) and median follow-up time with interquartile range. For models, we documented study type (development, internal/external validation), included predictors (including measurement methods, categorisation of continuous outcomes, blinding to outcome assessment and predictor variables), sample size (number of participants with events and included in modelling), statistical modelling methods (including fitting, missing data treatment and methods to adjust for overfitting), model performance (discrimination, calibration, sensitivity, specificity, net benefit and reclassification), model estimates and 95% confidence intervals (e.g. univariable unadjusted or adjusted estimates for predictors, adjusted coefficients for predictors in multivariable models). Where available, we extracted estimates with 95% confidence intervals including odds ratios, risk ratios and hazard ratios. The risk of bias for each included study was assessed via PROBAST (Prediction study Risk Of Bias ASsessment Tool). Domains were combined to give an overall risk of bias.

Where possible, participants with and without severe disease were extracted into 2 × 2 contingency tables. Studies were grouped for meta-analysis by effect estimates (e.g. odds ratios and hazard ratios) and meta-analysis was considered when there were three or more individual studies of a biomarker from which data using the same effect estimate could be extracted. We searched for predictor association with subsequent severe disease rather than exact estimates of strength or interpredictor comparisons. Studies were grouped for meta-analysis by prediction estimate type and by definition of severe disease, where possible. We grouped studies that were 'adequately adjusted', defined by clearly reported adjustment factors. Each study was included once per meta-analysis; where studies reported more than one estimate from the same participants using different definitions of severe disease, we selected the highest ranking. For example, estimates reporting surgery are preferentially included for meta-analysis as a higher-ranked estimate. Random-effects inverse variance meta-analysis was used to pool odds ratios. Meta-analysis was performed using 'metan' (Stata 14, StataCorp LP, TX, USA) because 2 × 2 contingency tables were not always available. Results were analysed across all ages, with groupings indicated on forest plots.

Results

A total of 29,947 abstracts were identified: 15,923 duplicates were removed and 14,024 abstracts were screened. In total, 247 full-text articles were assessed. Ultimately, 71 articles were included in the review, describing 56 non-overlapping patient cohorts. This included the addition of C-reactive protein, which was deemed important by the expert panel (other predictors identified by the panel were either already included or yielded insufficient data for meta-analysis). Most studies were European (37/71, 52%), with 14 (20%) studies from the USA/Canada. Forty (56%) studies were multicentre. In total, 36 (51%) studies were prospective, 33 (46%) were retrospective and two (3%) were unclear. Of the 71 studies, 11 (16%) were paediatric only, 23 (32%) were adult only and 37 (52%) were mixed. Recruitment dates varied, with 22 (31%), studies not reporting dates; follow-up also varied (median 8 years, interquartile range 5–10 years, range 0.8–18 years). Studies frequently presented several different definitions of severe disease. Most of the studies were rated as being at high risk of bias in at least one domain. Accordingly, 'Overall risk of bias' was rated as being 'high' in 65 (92%) studies. Only three studies were rated as being at a 'low' risk of bias. Overall, we identified 12 individual predictors that were eligible for meta-analysis: three serological, one genetic and eight clinical. There were no radiological, endoscopic or histological predictors that met a priori criteria for inclusion.

We were able to meta-analyse seven clinical markers from 58 studies. These were Montreal disease behaviour, age, disease duration, disease location, smoking, sex and family history. Meta-analysis of 12 studies (4376 participants, 1551 events) found that B2 stricturing, B3 fistulating, and either severe or disabling disease predicted severe disease more powerfully than B1 inflammation alone. B2 and B3 Montreal disease behaviours were the strongest predictors of subsequent severe disease in our review (B2: odds ratio 4.09, 95% confidence interval 2.59 to 6.48; B3: odds ratio 6.25, 95% confidence interval 3.68 to 10.63). Age at diagnosis was examined in 43 studies (19,623 participants, 7010 events). Most studies categorised age using Montreal/Vienna thresholds, so data were greatest for three groups: < 17 years, 17–40 years and > 40 years. Overall, diagnosis at < 17 years was associated with lower risk of subsequent severe disease than other ages. Disease duration was examined in 14 studies (8690 participants, 1714 events). Meta-analysis found that increased disease duration was associated with significant risk of subsequent severe disease at all durations examined. Disease location was examined in 32 studies (10,877 participants, 4193 events). Studies were diverse regarding the segments and/or segment combinations described. We were able to analyse 'colonic disease alone' and 'any colonic disease' versus other locations. Overall, colonic disease alone conferred significantly lower surgery risk (odds ratio 0.42, 95% confidence interval 0.31 to 0.58). Similarly, any colonic disease (23 studies, 7373 participants, 3086 events) predicted lower surgical or B2/B3 risk than no colonic disease. Perianal disease (24 studies, 13,483 participants, 5510 events) was associated with significantly increased risk of subsequent severe disease overall (1.84 odds ratio, 95% confidence interval 1.29 to 2.62). A total of 34 studies reported smoking associations (11,475 participants, 5097 events); meta-analysis of 26 studies found that current smoking increased risk significantly (odds ratio 1.53, 95% confidence interval 1.30 to 1.79). Sex was examined in 35 studies (14,489 participants, 5350 events) and was not a significant predictor overall. Family history was examined in 18 studies (5687 participants, 1413 events). Meta-analysis found no consistent direction and no significant association (odds ratio 1.05, 95% confidence interval 0.81 to 1.36).

Three serological markers (anti-*Saccharomyces cerevisiae* antibodies, anti-flagellin antibodies and C-reactive protein) from 13 studies were meta-analysed. Anti-*Saccharomyces cerevisiae* antibodies and anti-flagellin antibodies showed potential prognostic association. Anti-*Saccharomyces cerevisiae* antibody-positive patients had significantly increased odds of developing severe disease (odds ratio 2.29, 95% confidence interval 1.31 to 3.99, six studies). Anti-flagellin antibody data were identified in five studies; meta-analysis from odds ratios did not reach significance, but additional evidence from hazard ratios indicated significant association. For C-reactive protein, data were identified from only three studies (the expert panel requested C-reactive protein to be included) and the results found no significant predictive association. Of the genetic markers, results for nucleotide-binding oligomerisation domain-containing protein 2 (*NOD2*) in at least one variant were reported in 17 studies, although one study reported only *p*-values and was excluded from meta-analysis. Meta-analysis of 16 studies (5407 participants, 2645 events) suggested higher risk with a *NOD2* variant gene overall (odds ratio 1.69, 95% confidence interval 1.43 to 2.00).

Conclusions

During this review, we identified seven previous systematic reviews investigating the association of mostly serological and some genetic biomarkers with severe Crohn's disease. Three of these did not separate primary studies of diagnosis and prognosis. One review identified two studies of predictive biomarkers, one of which was also identified as the only prognostic study by a second review. The remaining systematic review included three biomarker prediction studies, only one of which met our inclusion criteria.

In summary, despite prognostic research being declared the greatest unmet need in Crohn's disease research and being faced with a vast amount of potential research, we could identify relatively few prognostic studies; just 56 non-overlapping patient cohorts were identified. Although a multitude of biomarkers were investigated, relatively few were examined individually in sufficient depth and

breadth for meta-analysis. Although genetic and serological biomarkers are perceived by clinicians as 'cutting edge', the reality is that we could identify only three that appeared genuinely prognostic: two serological (increased risk of developing severe disease was associated with anti-*Saccharomyces cerevisiae* antibodies and anti-flagellin antibodies positivity) and one genetic (*NOD2* variant gene positivity conveyed increased risk of developing severe disease). At the time of writing, this should help reassure clinicians that lack of access to novel biomarkers is not a major clinical disadvantage. We were able to identify five clinical biomarkers that appeared prognostic; the following were associated with increased risk of developing severe disease: Montreal B2/B3 disease behaviour versus B1, diagnosis at > 17 years of age, increased disease duration, disease beyond the colon and smoking.

Limitations

Our study does have limitations, predicated primarily by the quality of existing data. As noted already, despite being faced with a vast amount of potential research, we could identify relatively few prognostic studies. This paucity of genuine prognostic studies raises the possibility that our research is missing some clinically useful predictors simply because they have not been sufficiently studied (and so were discarded by our a priori quality criteria). This was the case for novel genetic and serological markers, the large majority of which were not studied by a sufficient number of primary studies to be eligible. Moreover, we were surprised that many apparently common predictors were not examined in sufficient depth; faecal calprotectin is one example. Furthermore, of those studies we were able to include, the majority were at high risk of bias, which will exert an effect on their results and, therefore, on the findings from our meta-analysis. A major frustration was that studies frequently confounded diagnosis and prognosis, which meant that our extraction was problematic.

There is also considerable existing excitement around multigene assays [e.g. PredictImmune Ltd (Cambridge, UK)] to predict severe disease, but these had been studied insufficiently for inclusion in our review and so could not be meta-analysed. Their recommendation will require either reporting in sufficient primary studies to allow meaningful meta-analysis or the publication of a prospective study of methodological quality such that meta-analysis of smaller, less rigorous studies becomes unnecessary.

Future work

The issue now turns to how to apply this review to the benefit of individual patients. Using existing data sets to which we have access, we are currently developing and validating a multivariable prognostic model that will combine the predictive factors identified so as to provide an estimate of the risk of subsequent severe disease for patients presenting with a new diagnosis of Crohn's disease. For obvious reasons, the model will not be applicable to those patients who present with severe disease. Contingent on the results of this validation, it may be clinically useful to perform an external validation in UK centres. In the meantime, we suggest that considerably more prognostic research in this area is required. The quality of this research and any multivariable models that arise should be improved by enhanced methodological rigour and adherence to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) reporting guidelines.

Study registration

This study is registered as PROSPERO CRD42016029363.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 45. See the NIHR Journals Library website for further project information.

Chapter 1 Background

The research detailed in this monograph is a response to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme call of 2014, HTA 14/210, 'Prognostic markers in early Crohn's disease'. Some of the text presented in this section has been published previously as part of the study protocol.[1]

The commissioning brief stated that the NHS decision problem turned on the fact that:

> *Some patients with Crohn's disease follow a relatively limited course with rapid response to relatively simple treatment and few subsequent acute flare-ups. Others progress rapidly to severe disease needing escalation of medical treatment or surgery: as many as one-third of patients require surgery within a year of beginning oral steroids. Rapid disease control may allow sufferers to return to work and other normal activities more rapidly and may reduce the need for surgery. NICE [National Institute for Health and Care Excellence] does not currently recommend early use of anti-TNF [tumour necrosis factor] drugs although there is some evidence of better early outcomes with their use. Rapid escalation of medical treatment is allowed for within current NICE guidelines. Identification of patients who might benefit from early intensive treatment is needed before the cost-effectiveness of treatment strategies can be determined.*
>
> *Reproduced with permission, 2021, NIHR HTA programme*[2]

The HTA programme stipulated that the commissioned research should comprise a systematic review that evaluated 'clinical criteria for treatment and/or use of biomarkers or biopsy informatics to develop a clinical tool to identify patients most likely to benefit from early intensive treatment'. Outcomes of the research would therefore be '[a]n overview of current evidence' combined with 'a signal as to which biomarkers may be most useful'. It was also noted that, contingent on the findings, any prediction tool that was developed during the research may be subsequently tested in a prospective study, in research commissioned by the HTA programme.

Crohn's disease and modern treatment strategy

Crohn's disease is an inflammatory ulcerative enteropathy that generally affects young adults and can be extremely debilitating. There is no cure and treatment is traditionally applied in a 'bottom-up' fashion, aimed at treating symptoms as and when they arise, with treatment escalated when symptoms worsen. However, newer biological therapies appear to ameliorate the ultimate disease trajectory in addition to treating symptoms. This attribute raises the possibility that adopting these agents early in a 'top-down' paradigm could 'stop the disease in its tracks'. The first disease-modifying biological agent was infliximab, which is a monoclonal antibody against the cytokine tumour necrosis factor (TNF) alpha that binds with it and prevents receptor binding. A randomised trial of infliximab versus placebo found that, of those patients who responded to an initial dose, half achieved complete mucosal healing after 1 year and stayed in remission longer and discontinued steroids earlier than control patients.[3] Biologicals also appear incrementally more effective when used in combination with other immunomodulators, such as azathioprine,[4] especially when administered in a 'top-down' fashion.[5,6] Newer agents, such as adalimumab, are also effective.[7]

The REACT (Early combined immunosuppression for the management of Crohn's disease) study randomised patients to either conventional 'bottom-up' therapy or 'early combined immunosuppression' and found that major complications, hospitalisation and surgery were significantly reduced at 24 months for the intervention clusters.[8] Accordingly, current thinking is that early aggressive biological treatment combined with immunomodulation will prevent future disease and is preferable to merely responding to symptoms. However, administering biologicals early to all patients is unwise because these agents may precipitate serious infection, are hepatotoxic and can cause demyelination, lupus syndrome and lymphoma.[9] Biologicals are also very expensive. A strategy that could identify new diagnoses of Crohn's disease who are destined to develop into severe disease in the future would have considerable clinical utility through 'personalised and targeted therapy', that is directing these patients to early biological treatment while avoiding unnecessary over-treatment in others.

Diagnostic and prognostic biomarkers of disease activity

According to the US National Institutes of Health, a biomarker is a measurable characteristic that indicates a biological process that may reflect pathology and pharmacological response to treatment.[10] Biomarkers in Crohn's disease may indicate the presence or absence of disease, as well as its severity. It is also important to understand the distinction between a 'diagnostic' biomarker and a 'prognostic' biomarker. While a reliable diagnostic biomarker may reflect the presence/absence/severity of current disease, a prognostic biomarker may reflect the presence/absence/severity of future subsequent disease (or of response to therapy, etc.). A clinically useful biomarker may be diagnostic, prognostic or a combination of both.

In our research, we have not been too restrictive when labelling an intervention or characteristic as a 'biomarker'. Although the term is associated with novel diagnostic technologies, simple and effective biomarkers have been used for decades. For example, stool frequency directly reflects colonic inflammation and should not be excluded from systematic review simply because it is not perceived as 'novel'. Smoking is believed to have a profound effect on disease outcome and should also be included, although smoking in and of itself is not a marker of disease activity. Several studies have investigated simple clinical factors that are predictive of an 'aggressive' disease course and Markov modelling of these factors has shown that disease activity over the year following diagnosis is predictive of the clinical course of the disease over the following decade.[11]

For the commissioned research we, therefore, aimed to identify the whole range of potential biomarkers used in Crohn's disease, including clinical (both clinician and self-reported outcomes), endoscopic, radiological, faecal, urinary, serological (including the range from basic tests to antibodies), genetic and histological biomarkers. For example, C-reactive protein (CRP) is an acute-phase protein expressed by the liver that is widely used in clinical practice. Calprotectin, a protein that is released in inflamed gut epithelium, is a more recent biomarker that has also reached daily practice. Calprotectin levels change with treatment. Lactoferrin is a similar protein biomarker. The diagnostic accuracy of such biomarkers has already been subject to systematic review and meta-analysis. For example, one such review[12] aimed to determine if calprotectin levels could differentiate between inflammatory and irritable bowel disease in children.

Chapter 2 Research questions

Our overarching research question was to identify biomarkers that are potentially able to predict which patients with Crohn's disease are destined to subsequently develop severe disease. This question (and related others) was answered through the research objectives listed below.

Primary research objective

1. To carry out a systematic review of the literature, including meta-analysis where possible, that covers all potential biomarker areas to assess their predictive capability for severe Crohn's disease. This review will determine the breadth, depth and quality of currently available evidence, and meta-analysis will identify which biomarkers may be sufficiently predictive for use in a subsequent prognostic model.

Secondary objectives

1. To compare potential predictors by direct and indirect comparison of study results. Direct comparisons between predictors from the same study constitute stronger evidence and will be preferred over indirect comparisons across different studies.
2. To explore heterogeneity among studies.
3. To identify those predictors that appear useful for the development and validation of a prognostic model to identify patients who are destined to develop severe Crohn's disease.
4. To examine and validate any existing models identified by the systematic review.

The ability to examine primary and secondary objectives will be highly dependent on the availability and quality of data from published studies.

Chapter 3 Review methods

At the design stage, we anticipated that there would be many potential biomarkers, which could make for an unwieldy review. We, therefore, set a priori quality/quantity thresholds for review inclusion to prevent extraction of data for biomarkers that have not been sufficiently studied for the findings to be deemed generalisable/reproducible and/or that have weak methodology. For example, at the time of writing the review protocol, more than 70 separate genes had been implicated in Crohn's disease.[13] Given that genetic sequencing is currently very expensive and there are multiple potential individual genetic predictors, we anticipated that few genetic predictors will have been studied in sufficient depth. However, sequencing will probably become increasingly cost-effective in the near future. Our systematic review, therefore, considered only those genes for which sufficient primary studies exist to provide a useful signal of their prognostic potential.

Genetic makeup is also linked to response to biological therapy. Given that genetic makeup is fixed, these factors need to be measured only once (in contrast to other biomarkers that fluctuate with disease activity). There are also multiple antibody candidates, and prognostic strategies have focused on both titres of individual antibodies and the number of different antibodies. For example, patients with three or more positive antibodies are eight times more likely to need surgery than patients who are antibody negative.[14]

Ethics review

Ethics permission is not required by our institution for systematic review of available medical literature.

Search strategy

The protocol for this research was published.[1] Our review question(s) and data extraction were guided by the CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) checklist.[15] Darren Boone, a clinical researcher experienced in systematic review and multidisciplinary Crohn's disease management, designed and carried out the search and was supervised by co-researchers, including statisticians with extensive prior experience of systematic review of prognostic markers (LA and SM), methodology experts (SH and SM) and disease experts (SH, TA, SB, MRJ and SAT). Uncertainties were resolved by face-to-face discussion.

Our scoping search found that individual studies frequently reported combinations of predictive biomarker groups.[1] For example, articles primarily reporting genetic predictors often included serological and/or clinical predictors. Therefore, we adopted an inclusive search strategy to identify all potential biomarker groups for severe Crohn's disease. We combined five clusters of search terms: (1) identification of Crohn's disease research; (2) identification of severe, disabling or complicated disease; (3) a panel of candidate biomarkers; (4) a panel of keywords and medical subject headings (MeSH) to identify prediction/prognosis; and (5) a panel of headings to exclude animal research, narrative reviews and editorials. Searches were combined using Boolean operators. We then tested the search string through its ability to identify key papers that were nominated by the authors. If unidentified, article keywords and MeSH were interrogated and the search string was refined until papers were captured. The search string used is shown in *Table 1*.

Search terms were identified by hand-searching Crohn's literature and guidelines from established clinical associations [e.g. the European Crohn's and Colitis Organisation (Vienna, Austria), the European Society of Gastrointestinal and Abdominal Radiology (Vienna, Austria)], and via a multidisciplinary panel.

TABLE 1 Search string used for the review

Search number	Search string	Number of hits on PubMed	Number of hits on EMBASE
1	(crohn*)	41,703	60,679
2	Aggressiv* OR Sever* OR Disabling OR Montreal OR Beaugerie OR Liege OR Flare OR Penetrat* OR Strictur* OR Resection OR Surgical OR Surgery OR Stoma OR Failure OR Active OR Adverse OR Harvey-Bradshaw OR HBI OR CDAI OR index OR Perianal OR Complex	6,329,437	4,441,705
3	Biomark* OR Marker OR Assay OR Imaging OR Radiolog* OR Genetic OR Examination OR Serum OR Blood OR Serolog* OR Stool OR Faecal OR fecal OR feces OR faeces OR Frequency OR Urin* OR Endoscop* OR histolog* OR histopathol* OR antibod* OR age OR Smoking OR Test	9,823,770	5,491,617
4	course OR prognos* OR outcome OR cohort OR progres* OR Predict* OR Risk* OR Outcome OR onset OR Biomarker* OR Natural history OR Predict*[tiab] OR Predictive value of tests[mh] OR Scor*[tiab] OR Observ*[tiab] OR Observer variation[mh] OR risk prediction model[tiab] OR predictive model[tiab] OR predictive equation[tiab] OR prediction model[tiab] OR risk calculator[tiab] OR prediction rule[tiab] OR risk model[tiab] OR statistical model[tiab] OR cox model[tiab] OR multivariable[tiab]OR validate OR nomogram OR predictive model OR validation OR prognostic model OR prognostic scor* OR prognostic index OR predictor OR diagnos*	7,516,769	5,683,139
5	Review[Publication Type] OR Bibliography[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR News[Publication Type]	2610	3843
6	1&2&3&4	13,905	22,498
7	6 NOT 5	11,295	18,655

Search process

Using the search string, Darren Boone queried the PubMed and EMBASE databases for literature published from inception to 1 January 2016 and screened the titles and abstracts of identified primary studies to assess their eligibility. Grey literature was identified by hand-searching conference proceedings from 2012–15, inclusive (European Crohn's and Colitis Organisation, United European Gastroenterology Week and Digestive Disease Week). An update was performed up to 1 January 2018 for serological biomarkers. We initially intended to search eight individual databases;[1] however, because our search of PubMed and EMBASE alone yielded nearly 30,000 citations, we decided that searching other databases would have been unduly burdensome in return for identifying little useful additional research.

Eligibility criteria

- Target condition: primary studies had to report patients with proven new or established diagnoses of Crohn's disease for which at least one biomarker was used to predict subsequent development of severe disease.
- Definition of Crohn's disease: diagnosis used standard clinical, endoscopic and pathological criteria. Studies reporting various severities were eligible if severe subgroups could be extracted.
- Participants: no age restriction was applied and paediatric studies (defined as aged < 16 years) were noted for subgroup analysis. All ethnicities, races and religious groups were eligible.

- Language: no language restriction was applied and translation was used where necessary.
- Inclusion criteria for biomarkers: to identify biomarkers with sufficient evidence, we stipulated that potential individual predictors must have been reported in at least five individual studies. We made an exception for 'new but exceptionally promising predictors', which were chosen by an expert panel from a list of all candidates identified by the review. The panel were also asked to indicate any predictor that was already in widespread use and which they deemed too important to be omitted from the review.
- Definitions of severe disease and outcomes: no universally accepted definition of 'severe' Crohn's disease exists. Surgery is often used as a surrogate for severe disease but, at the same time, early ileocolonic resection may be curative in some patients (and so these patients no longer have 'severe' disease). Immunomodulatory requirement as a surrogate for severe disease ignores the fact that some patients achieve complete mucosal healing and avoid complications, and that these drugs are used increasingly early in the disease trajectory. Although fistulae or penetrating disease form the backbone of the severe 'disease behaviour' domains of the Montreal,[16] Vienna[16] and Paris[17] classifications, perianal fistula is inconsistently considered, resulting in heterogeneous severity within those exhibiting 'complicated' features.

To avoid discarding potentially important research, we included studies that used a broad range of definitions. We also included studies that reported intestinal and perianal surgery [excluding appendicectomy, non-inflammatory bowel disease (IBD) surgery and simple perianal drainage]. Studies for which the end point was relapse or flare were excluded unless these aligned with our definitions of severe disease. Likewise, treatment change alone did not meet our criteria given that this is not necessarily associated with severe disease. We did not investigate lack of response to, for example, anti-tumour necrosis factor (anti-TNF) therapy or antibody development because these are related to treatment and are not in and of themselves surrogates for severe disease. Articles using treatment costs as surrogate for disease severity were excluded. *Table 2* shows varying definitions of severe disease from Beaugerie *et al.*,[18] Montreal behaviour classification,[19] Liege criteria[20] and the National Institute for Health and Care Excellence (NICE) Technology Appraisal (TA) 187.[21]

We stipulated a minimum of 3 months between biomarker measurement and outcome measurement to ensure that the biomarker was prognostic rather than diagnostic. Therefore, although studies exploring development of severe disease following intestinal surgery were eligible (noting that surgery would define severe disease in some classifications), prediction of early postoperative complications was excluded. Likewise, because the stability of serological markers changes over disease course,[22] we required contemporaneous serum draw and outcome measurement.

TABLE 2 Definitions of 'severe' disease

Beaugerie *et al.*[18] 'disabling disease'	Montreal behaviour classification[19]	Liege criteria[20]	NICE TA187[21]
Three or more steroid courses or steroid dependence; hospitalisation for flare or Crohn's disease complications; ≥ 12 months of disabling symptoms (nocturnal diarrhoea, urgency, abdominal pain, fever, fatigue, joint pain, uveitis or pyoderma); need for immunosuppression; intestinal resection; surgery for perianal disease	B1: inflammatory; B2: stricturing; B3: penetrating (p = perianal modifier). B2/B3 = severe Crohn's disease	Complex perianal disease; any colonic resection; two or more SB resections (or a single SB resection of ≥ 50 cm); construction of a definitive stoma	CDAI score of ≥ 300 or Harvey–Bradshaw Index score of ≥ 8–9

CDAI, Crohn's Disease Activity Index; SB, small bowel.

Data extraction

Full-text articles were examined by Darren Boone and queries were initially raised with Lucinda Archer, followed by other collaborators where necessary. Ultimately, Sue Mallett examined all full-text articles selected for the review and verified data extraction, so that all results data were double screened and extracted. Data were extracted into a data sheet that incorporated measures developed from the CHARMS checklist[15] and Prediction model Risk Of Bias Assessment Tool (PROBAST),[23] with additional fields specific to our review.

We extracted author, journal, design (e.g. cohort, randomised controlled trial, retrospective database), methods, setting/context (organisation/service type, country), participants (including age, range, gender), time since diagnosis (symptom duration and/or time since diagnosis for established disease), markers of severe disease, symptom severity, disease location and burden, disease complications, Crohn's activity indices, surgical details, perianal disease and continence outcomes. In addition, we extracted data specific to the prognostic marker investigated, including measurement (methods, frequency), adverse events, reliability and reproducibility, and costs where available. We recorded study interventions and outcomes (including definitions, thresholds for severity/remission and whether or not they were prespecified) and median follow-up time with interquartile range (IQR).

For models, we documented study type (development, internal/external validation), included predictors (including measurement methods, categorisation of continuous outcomes, blinding to outcome assessment and predictor variables), sample size (number of participants with events and included in the modelling), statistical modelling methods (including fitting, missing data treatment, methods to adjust for overfitting), model performance (discrimination, calibration, sensitivity, specificity, net benefit, reclassification), model estimates and 95% confidence intervals (CIs) (e.g. univariable unadjusted or adjusted estimates for predictors, adjusted coefficients for predictors in multivariable models). Where available, we extracted estimates with 95% CIs, including odds ratios (ORs), risk ratios and hazard ratios.

Risk-of-bias assessment

The risk of bias (ROB) for each included study was assessed via PROBAST.[23] PROBAST has five broad domains: patient selection, predictors, outcome, sample size and participant flow, and analysis. Domains were combined to give an overall ROB.

Patient and public involvement

We included an 'expert' patient representative to help form our research proposal. The impact of patient and public involvement (PPI) was minimal in the systematic review and meta-analysis phases of this research given that data identification, extraction and analysis are largely independent of 'opinion'. However, as described in *Chapter 7*, we anticipate that PPI input will be vital for future research because a non-medical perspective will be required to implement any model in daily clinical practice. Weighting the presumed benefits of early biological treatment against the risk of side effects must be considered against the predictive capabilities of the model, all from a patient perspective.

Statistical analysis

Where possible, participants with and without events (i.e. severe disease) were extracted into 2 × 2 contingency tables for each study. The number of studies and effect estimates for each predictor are reported in *Table 7*. Studies were grouped for meta-analysis by their effect estimates (e.g. ORs and hazard ratios). Meta-analysis was considered when there were three or more individual studies of a biomarker from which data could be extracted using the same effect estimate.

We looked for predictor association with subsequent severe disease rather than precise estimates of strength or interpredictor comparison. We anticipated that varied designs would cause varied results; therefore, meta-analysis reflects evidence across all studies which provided informative data regarding specific situations, measurements and thresholds. Studies were grouped for meta-analysis by prediction estimate type and, where sufficient, by definition of severe disease. We grouped studies that were 'adequately adjusted', which was defined by clearly reported adjustment factors including at least one of the following confounders: age at diagnosis, perianal disease, steroids for first flare, disease location and/or behaviour, smoking, surgery and family history. Forest plots present study results (see *Figures 6–19*). Meta-analysis was considered for biomarkers with three or more studies using the same effect estimate; excessive heterogeneity precluded combination. Each study was included once per meta-analysis; where studies reported estimates at different definitions of severe disease, we selected the highest ranking (order: surgery, B2/B3, B3, B2, other definition). To avoid confounding, B2 and B3 were identified as predictors for which surgery was the outcome. We did not use B3 as a predictor for B3 or B2/B3 as an outcome.

Random-effect inverse variance meta-analysis[24] was used to pool ORs. Meta-analysis was performed using 'metan' (Stata 14, StataCorp LP, TX, USA) because 2 × 2 tables were not always available.

Owing to the paucity of results for children alone, results were analysed across all ages, with age groups indicated on forest plots.

Chapter 4 Studies included in the reviews

This review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; the PRISMA flow chart is illustrated in *Figure 1*. In total, 29,947 abstracts were identified (PubMed, $n = 11,292$; EMBASE, $n = 18,655$). A total of 15,923 duplicates were removed and 14,024 abstracts were screened. After applying the eligibility criteria, 247 full-text articles were assessed, which included four of the biomarkers that were considered essential by the expert panel. Ultimately, 71 articles were included in the review, which corresponded to 56 non-overlapping patient cohorts. Reasons for exclusions are given in *Figure 1*.

Table 3 shows the predictors that were deemed important for meta-analysis by the expert panel. Ultimately, this involved the addition of only one predictor: CRP. Nine predictors that were deemed important were already included. Seven predictors that were deemed important yielded too few individual studies to be viable for meta-analysis. For example, there were no prognostic studies of faecal calprotectin. 'Severe endoscopic lesions' were deemed important but prognostic data were provided by only two studies.

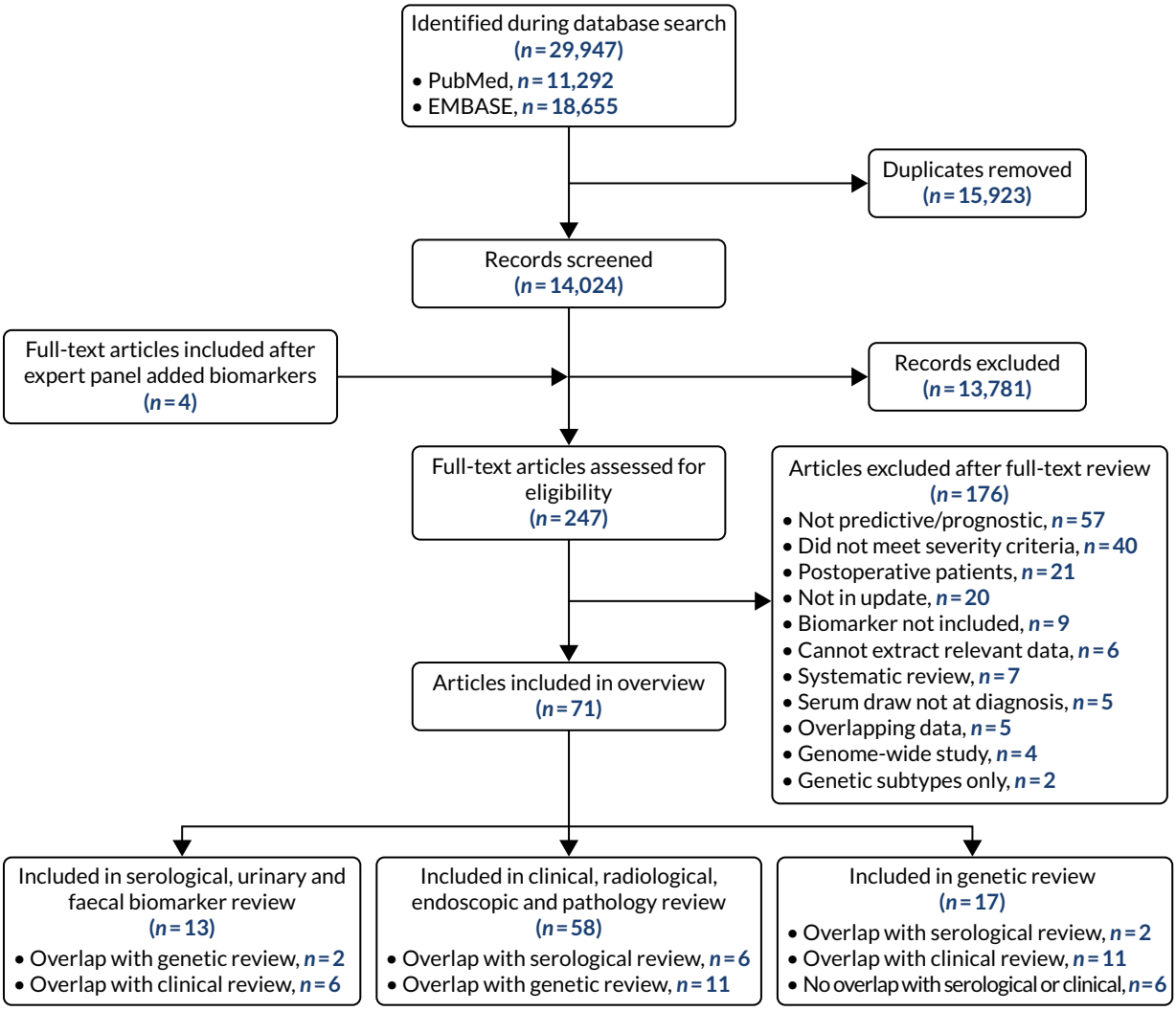

FIGURE 1 The PRISMA flow chart. Some articles were included in more than one review. a, Hand-searching of conference proceedings failed to yield any additional research.

TABLE 3 Predictors considered by the expert panel

Factor chosen by the experts	Inclusion in overview
CRP	Added
Azathioprine/biologicals	Confounding treatment
Use of TPN	Confounding treatment
Low adherence to medication	Confounding treatment
Upper disease	'Location' included already
Bowel stenosis	Included already
Internal fistula	Included already
Stricture	Included already
Development of strictures during follow-up	Included already
Development of fistulae during follow-up	Included already
Jejunal involvement	Included already
ASCA-IgG	Included already
ASCA-IgA	Included already
Flares per year	Insufficient to include ($n = 0$)
Faecal calprotectin	Insufficient to include ($n = 0$)
Weight loss	Insufficient to include ($n = 1$)
FOXO3a	Insufficient to include ($n = 1$)
Systematic manifestations	Insufficient to include ($n = 2$)
Severe endoscopic lesions	Insufficient to include ($n = 2$)
Albumin	Insufficient to include ($n = 2$)
Ethnic origin	Insufficient to include and diverse ($n = 2$)

ASCA, anti-*Saccharomyces cerevisiae* antibodies; IgA, immunoglobulin A; IgG, immunoglobulin G; TPN, Total Parenteral Nutrition.

Ultimately, the number of papers included in the three reviews were as follows:

- general overview – 58 papers (including 11 contained in the genetic review and six in the serological review)
- genetic review – 17 papers (including 11 contained in the general overview and two in the serological review)
- serological review – 13 papers (including six contained in the general overview and two in the genetic review).

Chapter 5 Results of the reviews

Most of the studies were European (37/71, 52%), with 14 (20%) from the USA/Canada. A total of 40 (56%) studies were multicentre (*Table 4*). In total, 36 (51%) studies were prospective, 33 (46%) were retrospective and two (3%) were unclear. Of 71 studies, 11 (16%) were paediatric only, 23 (32%) were adults only and 37 (52%) were mixed. Individual study characteristics are shown in *Table 4*.

The recruitment dates varied (see *Table 4*), with 22 (31%) studies not reporting recruitment dates. Follow-up also varied (median 8 years, IQR 5–10 years, range 0.8–18 years; *Table 4*). Nine studies allowed extraction of prediction of severe disease events at multiple time points during follow-up.[25–33] Studies frequently presented several definitions of severe disease (*Table 5*).

TABLE 4 Overview of study characteristics

Study characteristic	Total studies ($N = 71$)
Prospective study design ($n = 36$)	
Prospective clinic	17
Prospective cohort	8
Prospective inception cohort	1
Prospective registry	10
Retrospective study design ($n = 33$)	
Retrospective cohort	5
Retrospective clinic notes	17
Retrospective registry, databank	8
Retrospective case–control	3
Unclear study design	2
Multicentre	40
Region	
Europe	38
USA/Canada	14
Other	19
Participants	
Children only	11
Children and adults	37
Adults only	23
Recruitment dates reported	49
Number of patients, median (IQR) [range]	248 (159–555) [70–3118]
Number of events (severe disease), median (IQR) [range][a]	76 (51–70) [14–981]
Follow-up (years), median (IQR) [range]	8 (5–10) [0.8–18]

IQR, interquartile range.
a Events calculated as mean of smallest and largest number of events per study.

TABLE 5 Individual study characteristics

Study (first author and year)	Country	Multicentre	Study design	Dates of recruitment	Follow-up and range (years)	Follow-up statistics	Number of participants	Number of events		Definition of serious disease	Adults and/or children	Marker		
								Minimum	Maximum			Serology	Genetic	Clinical
Aldhous 2007[34]	Scotland	No	Prospective clinic	NR. Pre-2007	10 (0.3–55)	Median (range)	274	105	113	Surgery, B2/B3	Adults	No	No	Yes
Alvarez-Lobos 2005[35]	Spain	No	Prospective clinic	2002–4	7.4 (SD 6.1)	Mean (SD)	159	59	70	Surgery	Adults	No	Yes	No
Annese 2005[36]	Italy	Yes	Prospective cohort	NR. Pre-2005	Sporadic 7 (SD 4); familial 9 (SD 6)	Mean (SD)	316	87	151	Surgery	Adults	Yes	Yes	Yes
Beaugerie 2006[18]	France	No	Retrospective clinic records	1985–98	5	Fixed time period	1123	957	957	Other	Both	No	No	Yes
Brant 2003[37]	USA	Yes	Retrospective genetic cohort	NR. Pre-2003	B1 > 8	Minimum time for B1	257	49	183	Surgery	Adults	No	Yes	Yes
Büning 2004[38]	Germany	No	Prospective clinic	NR. Pre-2004	6 (SD 7.0)	Mean (SD)	180	51	51	Surgery	Adults	No	Yes	No
Charpentier 2014[39]	France	Yes	Retrospective from registry	1988–2006	6 (2–11)	Median (range)	367	103	103	Surgery	Adults	No	No	Yes
Chatzicostas 2006[40]	Greece	Yes	Prospective registry, with additional clinic cohort	NR. Pre-2006	10.5 (SD 6.4)	Mean (SD)	80	38	38	B2/B3	Both	No	No	Yes
Chen 2015[41]	The People's Republic of China	No	Retrospective clinic database	1992–2012	7 (0–19)	Median (range)	197	37	64	Surgery	Both	No	No	Yes
Choung 2016[42]	USA	Yes	Prospective registry	1990–NR (pre-2015)	6.0 (IQR 5.6–8.1)	Median (IQR)	100	21	24	Other	Adults	Yes	No	Yes
Cleynen 2013[43]	EU[a]	Yes	Retrospective hospital clinics	NR. Pre-2015	18 (10–62)	Median (range)	1528	600	844	Surgery	Both	No	Yes	Yes
Degenhardt 2016[44]	Germany	No	Retrospective serum bank	2000–6	12	Median	70	20	20	Other	Adults	Yes	No	No
Dubinsky 2008[45]	USA	Yes	Unclear. 21 hospital sites	NR. Pre-2008	2.5 (0.1 to 19.6)	Median (range)	592	37	61	Surgery, B2/B3	Children	Yes	No	No
Goel 2013[46]	India	No	Retrospective clinic records	1995–2008	1.5 (0.1–16.5)	Median (range)	223	73	93	Surgery, B2/B3	Adults	No	No	Yes
Gupta 2006[47]	USA	Yes	Prospective registry	2000–3	3.6 (SD 3.1)	Mean (SD)	989	128	128	Surgery	Children	No	No	Yes
Henckaerts 2009[48]	Belgium	Yes	Retrospective registry	1996–2009	14 (IQR 7–22)	Median (IQR)	666	349	432	Surgery	Adults	No	Yes	Yes

Study (first author and year)	Country	Multicentre	Study design	Dates of recruitment	Follow-up and range (years)	Follow-up statistics	Number of participants	Number of events		Definition of serious disease	Adults and/or children	Marker		
								Minimum	Maximum			Serology	Genetic	Clinical
Israeli 2014[25]	Canada	No	Retrospective clinic records	1993–2012	11.1 (1–58)	Median (range)	379	19	167	Surgery	Both	No	No	Yes
Jauregui-Amezaga 2015[49]	Spain	No	Prospective clinic	2007–11	4.1 (1.8–5.4)	Median (IQR)	112	29	29	Surgery	Both	Yes	No	Yes
Kugathasan 2017[50]	USA and Canada	Yes	Prospective inception cohort	2008–12	3.6 (3–4.3)	Unclear	913	78	78	B2/B3	Children	Yes	No	No
Kugathasan 2004[51]	USA	No	Prospective clinic	2003	3.3 (0.5–7.3)	Mean (range)	138	49	49	B2/B3	Children	No	Yes	No
Kwon 2016[52]	The Republic of Korea	Yes	Retrospective clinic records	1982–2008	7.1 (3.1–10.8)	Median (unclear)	705	156	156	Surgery	Both	Yes	No	No
Lacher 2010[53]	Germany	No	Prospective clinic	2000–9	4.8 (0.3–13.1)	Mean (range)	171	32	32	Surgery	Children	No	Yes	No
Laghi 2005[54]	Italy	No	Retrospective clinic records	NR. Pre-2005	10.1 (SD 8.1)	Mean (SD)	193	145	187	Surgery	Adults	No	Yes	Yes
Lakatos 2005[55]	Hungary	Yes	Prospective cohort	2003–5	8.2 (3.2–13.2)	Unclear	527	220	311	Surgery	Adults	No	Yes	No
Lakatos 2009[56]	Hungary	No	Retrospective clinic records	NR. Pre-2009	9.4 (1.9–16.9)	Unclear	198	61	61	B2/B3	Adults	No	No	Yes
Law 2013[57]	The People's Republic of China	No	Retrospective clinic records	2000–12	8 (5)	Median (IQR)	79	22	34	Surgery, other	Both	No	No	Yes
Loly 2008[20]	Belgium	Yes	Retrospective clinic records	NR. Pre-2006	5	Minimum follow-up	361	135	209	Other	Both	Yes	No	Yes
Louis 2003[26]	France	No	Prospective clinic	NR. Pre-2001	No information		90	18	53	B2/B3	Both	Yes	Yes	Yes
Lovasz 2013[27]	Hungary	Yes	Prospective cohort	1977–2008	13.5 (6–19.5)	Median (IQR)	287	33	110	B2/B3	Both	No	No	Yes
Lunney 2015[58]	Australia	Yes	Prospective registry	1955–2012	9 (3–16)	Median (IQR)	622	212	212	Surgery	Both	No	No	Yes
Malmborg 2015[59]	Sweden	Yes	Retrospective clinic records	1990–2007	8.8 (1.0–20.8)	Median (range)	161	25	25	B2/B3/ surgery	Children	No	No	Yes
Mazor 2011[60]	Israel	No	Prospective clinic	2000–10	12	Mean	146	65	65	B2/B3/ surgery	Both	No	No	Yes
Moon 2014[61]	The Republic of Korea	Yes	Retrospective hospital clinics	1987–2012	4.4 (2.8)	Mean (SD)	728	126	126	Surgery	Adults	No	No	Yes

continued

TABLE 5 Individual study characteristics (*continued*)

Study (first author and year)	Country	Multicentre	Study design	Dates of recruitment	Follow-up and range (years)	Follow-up statistics	Number of participants	Number of events		Definition of serious disease	Adults and/or children	Marker		
								Minimum	Maximum			Serology	Genetic	Clinical
Nasir 2013[62]	New Zealand	Yes	Retrospective genetic case–control	2003–13	9	Mean	503	240	240	Surgery	Both	No	Yes	Yes
Nasir 2013[63]	New Zealand	Yes	Retrospective genetic case control	2003–13	9	Mean	503	240	240	Surgery	Both	No	Yes	Yes
Nunes 2013[64]	Spain	Yes	Retrospective registry	NR. 2006–	7.6 (3–13)	Median (IQR)	3118	649	1313	Surgery, B2	Adults	No	No	Yes
Odes 2001[65]	Israel	Yes	Prospective cohort	NR. Pre-2000	7.1 (8.0)	Mean (SD)	208	64	64	Surgery	Adults	No	No	Yes
Oh 2017[66]	The Republic of Korea	No	Prospective registry	2008–10	7.9 (6.8–8.0)	Median (IQR)	339	59	59	Surgery	Adults	Yes	No	No
Oriuchi 2003[67]	Japan	No	Retrospective clinic records	1965–98	9.9 (7.5)	Mean (SD)	146	44	44	Surgery	Both	No	No	Yes
Pandey 2015[68]	Singapore	Yes	Retrospective clinic records	1970–2013	7.3 (2.9–13.0)	Median (range)	430	75	112	Surgery	Both	No	No	Yes
Papi 2005[69]	Italy	No	Retrospective clinic records	1993–2001	4.84 (1–23.2)	Mean (range)	139	47	47	B3	Both	No	No	Yes
Park 2013[70]	The Republic of Korea	No	Retrospective registry	1989–2010	5.4	Median	1403	471	471	Surgery	Both	No	No	Yes
Pigneur 2010[71]	France	Yes	Retrospective registry	2000–7	14.7 (10.8–45.2)	Median (range)	618	374	374	Surgery	Both	No	No	Yes
Pittet 2013[28]	Switzerland	Yes	Retrospective clinic cohort	2006–13	> 10	Range	1026	83	463	Surgery	Both	No	No	Yes
Polito 1996[72]	USA	No	Retrospective clinic records	1985–91	14	Mean	555	85	334	Surgery	Both	No	No	Yes
Posovszky 2013[73]	Germany	No	Prospective clinic	NR. Pre-2013	15 (11)	Mean (SD)	202	30	109	Surgery	Both	No	Yes	Yes
Protic 2008[74]	Serbia	No	Prospective clinic	2005–6	7 (0–30)	Median (range)	131	33	81	Surgery	Adults	No	Yes	No
Renda 2008[75]	Italy	No	Prospective clinic	NR. Pre-2008	6.2	Median	182	110	110	Surgery	Both	No	Yes	Yes
Rieder 2010[76]	Germany	No	Prospective clinic	2000–6	0.8 (0.1–4.4)	Median (IQR)	76	14	14	Surgery	Adults	Yes	No	No
Romberg-Camps 2009[77]	The Netherlands	Yes	Prospective registry	1991–2003	7.5 (0.2–15.4)	Median (range)	476	133	207	Surgery	Both	No	No	Yes

Study (first author and year)	Country	Multicentre	Study design	Dates of recruitment	Follow-up and range (years)	Follow-up statistics	Number of participants	Number of events		Definition of serious disease	Adults and/or children	Marker		
								Minimum	Maximum			Serology	Genetic	Clinical
Ryan 2013[78]	Canada	Yes	Prospective registry	NR. Pre-2013	9.3	Median	86	21	100	Surgery	Adults	Yes	No	Yes
Sabate 2008[79]	France	No	Prospective clinic	2001–2	9.3 (7.7)	Mean (SD)	225	83	83	B2	Adults	No	No	Yes
Sands 2003[80]	USA	Yes	Retrospective clinic cohort	1991–7	3	Minimum follow-up	251	40	69	Surgery	Both	No	No	Yes
Savoye 2012[81]	France	Yes	Retrospective registry	1988–2004	8 (7–12)	Median (range)	309	115	237	Other	Children	No	No	Yes
Schaefer 2010[82]	USA	Yes	Prospective registry	2002–8	2.0 (1.8–2.3)	Median (IQR)	845	57	72	Surgery	Children	No	No	Yes
Shaoul 2009[83]	Israel	Yes	Prospective clinic	NR. Pre-2009	4.9 (3.6)	Mean (SD)	121	28	38	Surgery, B2/B3	Children	No	Yes	Yes
Siegel 2011[84]	USA	Yes	Unclear. 21 hospital sites	NR. Pre-2008	2.8 (0.1–19.6)	Median (range)	579	67	67	B2/B3	Children	No	No	Yes
Siegel 2016[85]	USA	No	Prospective clinic	NR. Pre-2015	6.1 (0.3–15)	Median (range)	243	142	142	B2/B3/ Surgery	Adults	Yes	No	Yes
Smith 2004[29]	Scotland	No	Prospective clinic	NR. Pre-2004	11.5 (6.7–20)	Median (IQR)	90	28	62	B2/B3	Adults	No	Yes	Yes
Solberg 2007[86]	Norway	Yes	Prospective cohort	1990–4	10.3 (9–12)	Median (range)	237	34	85	Surgery	Both	No	No	Yes
Solberg 2014[30]	Norway	Yes	Prospective cohort	1990–4	10	Minimum follow-up	111	48	77	B2/B3/ surgery	Both	No	No	Yes
Song 2011[87]	The People's Republic of China	No	Retrospective clinic cohort	2000–9	4 (1–21)	Median (range)	167	42	79	Surgery	Both	No	No	Yes
Tarrant 2008[88]	New Zealand	Yes	Retrospective genetic case–control	2003–5	6.5 (0.1–65)	Median (range)	715	50	85	B2/B3	Both	No	No	Yes
Thia 2010[89]	USA	Yes	Retrospective cohort	1970–2004	8.5 (0.01–36)	Median (range)	248	50	139	B2/B3	Both	No	No	Yes
van der Heide 2009[90]	The Netherlands	No	Prospective clinic	1995–2005	9.4 (4.9–19.0)	Median (IQR)	258	130	220	B2/B3	Both	No	No	Yes
Van Limbergen 2008[31]	Scotland	Yes	Prospective cohort	2000–8	Adult 10.3 (3.8–20.6); children 3.7 (1.7–6.0)	Median (IQR)	774	100	305	Surgery	Both	No	No	Yes

continued

TABLE 5 Individual study characteristics (*continued*)

Study (first author and year)	Country	Multicentre	Study design	Dates of recruitment	Follow-up and range (years)	Follow-up statistics	Number of participants	Number of events		Definition of serious disease	Adults and/or children	Marker		
								Minimum	Maximum			Serology	Genetic	Clinical
Vernier-Massouille 2008[91]	France	Yes	Prospective registry	1988–2002	7.0 (4.3–10.3)	Median (range)	394	176	176	Surgery	Children	No	No	Yes
Vester-Andersen 2014[92]	Denmark	Yes	Prospective cohort	2003–4	7.7 (7.1–8.4)	Median (IQR)	213	49	49	Surgery	Both	No	No	Yes
Yaari 2016[93]	Israel	No	Retrospective clinic records	2006–14	1	Minimum follow-up	126	59	59	Surgery	Both	Yes	No	No
Yang 2011[32]	The People's Republic of China	Yes	Retrospective clinic records	NR. Pre-2011	NR		207	147	166	Other	Both	No	No	Yes
Zabana 2013[33]	Spain	Yes	Prospective registry	1994–2003	7.6 (5.8–11.6)	Median (IQR)	246	43	109	Surgery	Both	No	No	Yes

EU, European Union; NR, not reported; SD, standard deviation.
a Italy, France, the UK, Czechia, the Netherlands, Belgium, Spain and Germany.
Notes
Number of events refers to the number of patients with severe disease in a study. Maximum and minimum values are given as the same study may have different numbers of patients with severe disease for the different definitions of severe disease, and for different predictors.

The forest plots for predictors indicate data characteristics, including event, paediatric versus adult versus mixed population, and whether or not patients with severe disease were included at baseline. For each predictor meta-analysis, we ensured that patients were included in analyses only once. *Figure 2* presents the ROB summarised across all studies.

Most of the studies were rated as having high ROB in at least one domain. Accordingly, 'Overall ROB' was rated as 'high' in 65 (92%) studies. Only three studies were rated as having 'low'[59,89,91] ROB and three were rated as 'unclear'.[28,58,79] Concern regarding 'Overall applicability' was rated as 'low' or 'unclear', except for five studies.[30,46,60,67,73] ROB and applicability for individual studies are presented in *Box 1* and *Figures 3–5*.

Overall, we identified 12 individual predictors eligible for inclusion: three serological, one genetic and eight clinical. There were no radiological, endoscopic or histological predictors that met our criteria for inclusion in the review.

Paediatric data are presented in the forest plots, but there were insufficient for subgroup analysis.

Table 6 shows the summary of findings across the meta-analyses performed.

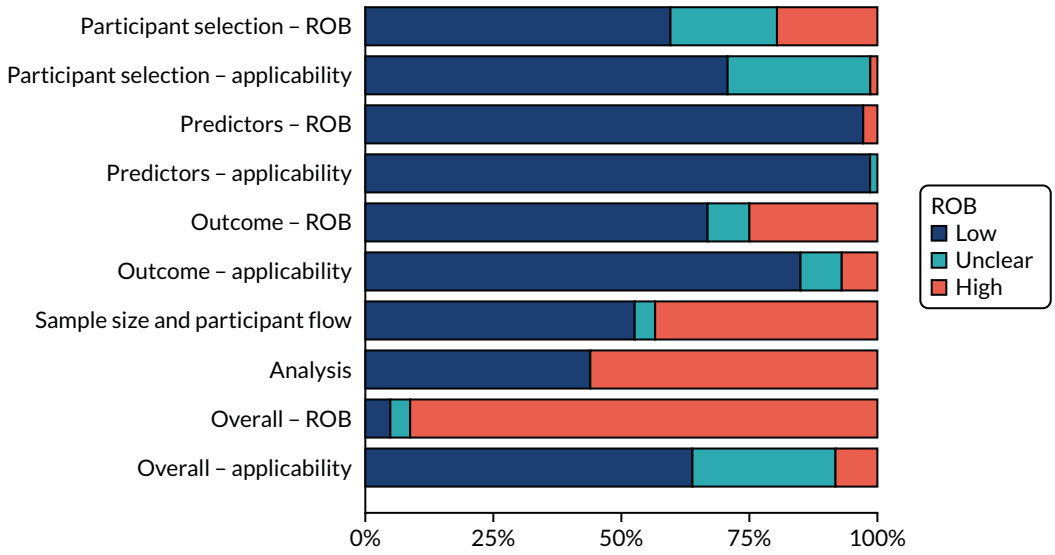

FIGURE 2 Risk of bias summarised across all studies.

BOX 1 Summary by domain of ROB and concerns relating to the applicability to the review question

Participant domain

Low ROB ($n = 41$) was determined when patients with severe disease could be excluded at baseline in data extraction ($n = 42$) and the study design was not a case–control design ($n = 68$). Results are at ROB when included patients have severe disease at baseline ($n = 12$ included; $n = 16$ unclear), as the results refer to a mixture of prediction of severe disease and risk of diagnosis.

Fifty studies were rated as being of low concern for applicability. Twenty studies were rated as unclear because of poor reporting and one study was rated as being of high concern owing to restricting enrolment to Indian patients who had received previous antituberculous therapy.

BOX 1 Summary by domain of ROB and concerns relating to the applicability to the review question (*continued*)

Predictor domain

Low ROB, for which measurement of predictors would not cause ROB, was identified in 69 studies. In two studies,[66,78] there is a potential ROB related to serological biomarker measurement because of the time of serum collection.

Seventy studies were rated as being of low concern for predictor assessment applicability. One study[78] was rated as unclear for applicability because over 50% of patients had severe disease at enrolment when the serum sample was taken.

Outcome domain

Forty-seven studies were rated as being at a low ROB. Studies were rated as at a high ROB when the definition of severe disease did not correspond to our standard definitions, sometimes included steroid dosing ($n = 7$), or where perianal surgery was included as surgery ($n = 12$).

Sixty-one studies were rated as being of low concern for outcome applicability, six were rated as being unclear for applicability of outcome definitions because of poor reporting and four were rated as being of high concern as a result of less relevant outcome definitions.

Flow and timing domain

Thirty-seven studies had a low ROB rating, based on an average time to event of 5–10 years and more than 20 events in the analysis. A total of 31 studies were rated as being at high ROB (studies could be rated as at high ROB for more than one reason): 30 studies because the average time to event was not between 5 and 10 years, two studies, in addition, had fewer than 20 events; and one study's time to event was unclear as well as having fewer than 20 events. In three studies, the ROB was unclear as time to event was unclear and there were more than 20 events in the analysis.

Applicability is not assessed for this domain.

Analysis domain

Thirty-one studies were rated as being at low ROB in the analysis because non-significant results were reported for at least three standard predictors. Forty studies were rated at high ROB because fewer than three standard predictors were reported with significant results. Standard predictors were defined as those included in this overview.

Applicability is not assessed for this domain.

Overall

Three studies were rated as being at low ROB in all domains[59,89,91] and in three the ROB was unclear.[28,58,79] A total of 65 studies were rated as being at high ROB in at least one domain, mostly owing to ROB in either flow and timing, or the analysis domain.

Forty-five studies were rated as having an overall low concern for applicability, with 21 having an unclear rating and five having a high concern for applicability in at least one domain. The studies that were rated as having a high concern were four studies with composite outcomes defined in a slightly non-standard way and one study that enrolled Indian patients who had received antituberculous therapy only.

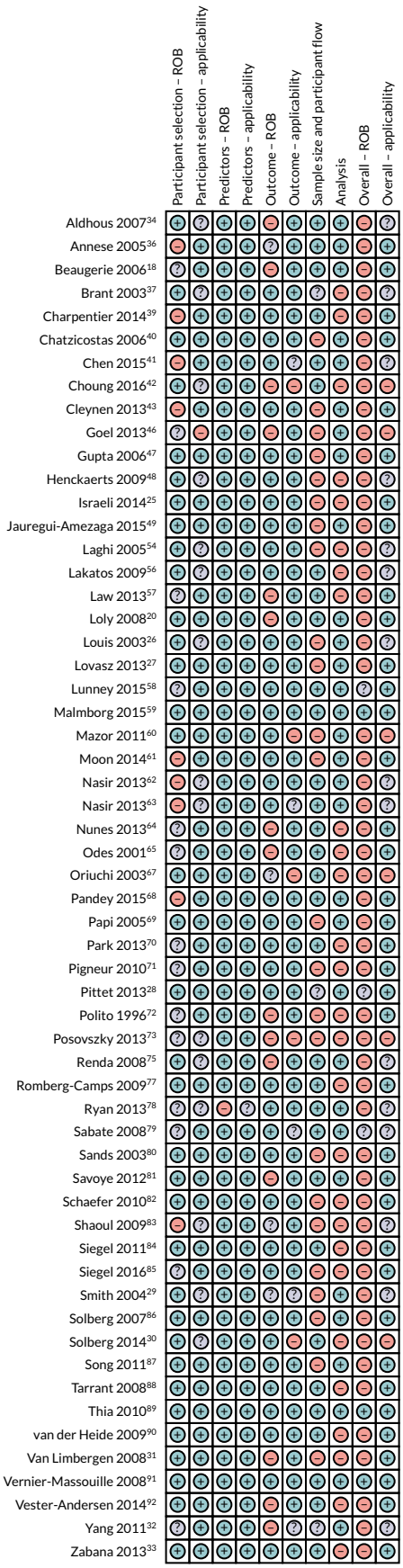

FIGURE 3 Risk-of-bias and applicability concerns summary: review of author judgements regarding each domain for each individual study in the clinical review. Orange circles indicate high ROB; blue circles indicate low ROB; purple circles indicate uncertain ROB.

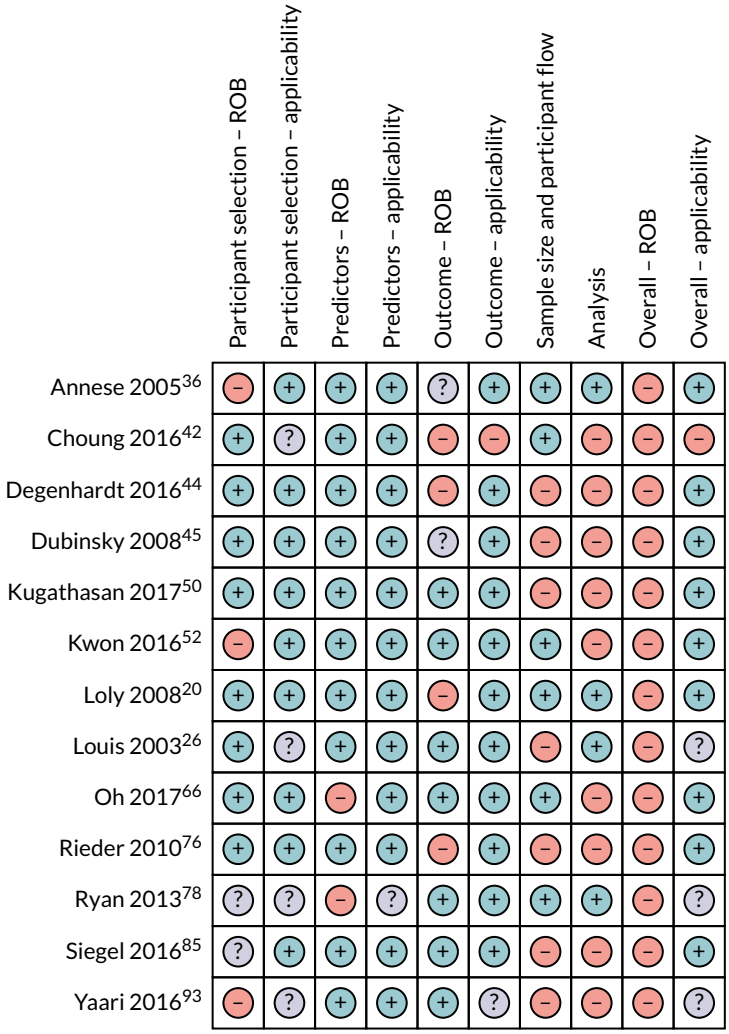

FIGURE 4 Risk-of-bias and applicability concerns summary: review of author judgements regarding each domain for each individual study in the serological review. Orange circles indicate high ROB; blue circles indicate low ROB; purple circles indicate uncertain ROB.

Meta-analysis of clinical predictors

The following clinical predictors had prognostic data available from fewer than five studies and, therefore, did not meet the inclusion criteria for the review: submucosal plexitis, fever, weight loss, poor growth, medication, upper disease, Jewish ethnicity, joint problems, abdominal pain, oral contraception (women), ethnic origin, systematic manifestations, systematic steroid use, azathioprine/biologicals, granuloma, depression, cancer, diarrhoea, time to diagnosis from symptom onset, severe endoscopic lesions, visceral fat area, rectal bleeding, fatigue, use of total parenteral nutrition, bowel stenosis, internal fistula, alternative initial diagnosis, abscess, stricture, development of strictures during follow-up, development of fistulae during follow-up, initial diagnosis at surgery, steroids per year, flares per year, married/common law, low conscientiousness, high neuroticism, low adherence to medication, adverse childhood experience, childhood sexual abuse, childhood physical abuse, high childhood adversity score, asthma, eczema, glandular fever, kidney stones, liver disease, mental illness, bronchiectasis, tonsillectomy, chole, grommet, immunised against measles, immunised against mumps, immunised against tuberculosis, antibiotic consumption, medication consumption, breastfed, alcohol, vegetarian, takeaways, public swimming, sand pit, farm, shared bedroom, continuous course, frequent relapse, symptoms at diagnosis,

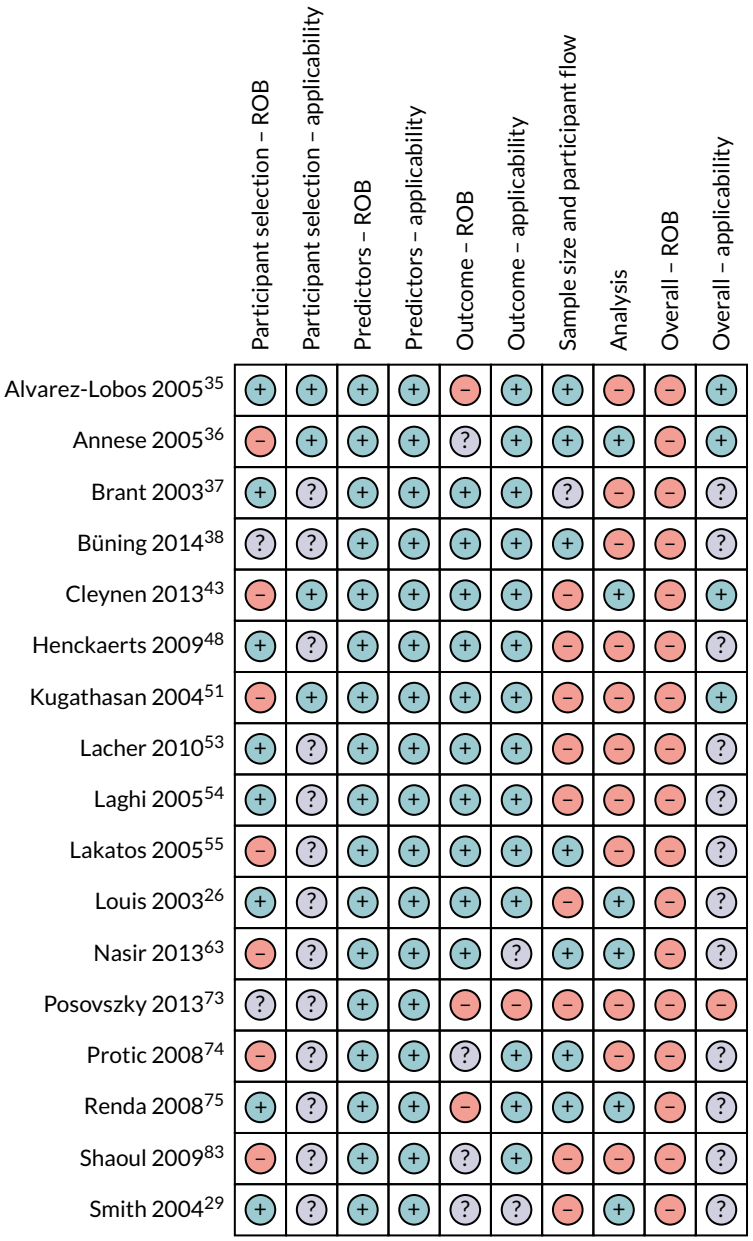

FIGURE 5 Risk-of-bias and applicability concerns summary: review of author judgements regarding each domain for each individual study in the genetic review. Orange circles indicate high ROB; blue circles indicate low ROB; purple circles indicate uncertain ROB.

symptoms at 1 year, persistent mucosal erosions, jejunal involvement, Crohn's Disease Activity Index (CDAI), educational level, type of centre, nausea/vomiting, diabetes mellitus, coronary artery disease and hypertension.

We were able to meta-analyse seven clinical markers from 58 studies. These were Montreal disease behaviour, age, disease duration, disease location, smoking, sex and family history.

A meta-analysis of 12 studies (4376 participants, 1551 events) found that B2 stricturing, B3 fistulating and either severe or disabling disease predicted severe disease more powerfully than B1 inflammation alone (see *Table 6* and *Figure 6*). B2 and B3 Montreal disease behaviours were the strongest predictors of subsequent severe disease in our review (B2: OR 4.09, 95% CI 2.59 to 6.48; B3: OR 6.25, 95% CI 3.68 to 10.63).

TABLE 6 Summary of findings table

Biomarker	Overall number of participants; events expressed as minimum (studies)	Estimates reported[a]	Meta-analysis estimate (95% CI); *n* studies	Notes
ASCA	2559; 369 (10)	• OR, *n* = 6 • HR, *n* = 2 • Adj HR, *n* = 1 • *p*-value, *n* = 2	OR 2.29 (1.31 to 3.99), 6	Five studies report increased severe disease with presence of ASCA
Anti-CBir1	1878; 302 (5)	• OR, *n* = 3 • HR, *n* = 2	OR 1.91 (0.85 to 4.31), 3	Two studies report increased risk with presence of anti-CBir1
CRP	1170; 274 (3)	• OR, *n* = 3	OR 1.17 (0.85 to 1.61), 3	Two studies report increased severe disease with presence of CRP
NOD2 any variant	5526; 2683 (17)	• OR, *n* = 16 • *p*-value, *n* = 1	Surgery OR 1.69 (1.43 to 2.00), 16	14 studies report increased severe disease with presence of the *NOD2* variant
Disease behaviour	8678; 3142 (16)	• OR, n = 12 • Adj HR, *n* = 2 • *p*-value, *n* = 2	• B2: OR 4.09 (2.59 to 6.48), 11 • B3: OR 6.25 (3.68 to 10.63), 10 • B2/B3: OR 6.58 (4.18 to 10.38), 9	All studies report increased severe disease with presence of B2, B3 or B2/B3 compared with B1
Age at diagnosis	19,623; 7010 (43)	All age data: • OR, *n* = 29 • Adj OR, *n* = 3 • HR, *n* = 5 • Adj HR, *n* = 2 • *p*-value, *n* = 6	• < 17 years to ≥ 17 years: OR 0.71 (0.52 to 0.98), 15 • < 17 years to 17–40 years: OR 0.59 (0.35 to 1.01), 8 • > 40 years to ≤ 40 years: OR 0.67 (0.38 to 1.17), 8	Age comparisons limited by data cut-off points reported in studies. Aged < 17 years at diagnosis has lower OR for severe disease than that for older age
Duration of disease	8690; 1714 (14)	All time points: • OR, *n* = 22 • HR, *n* = 1 • *p*-value, *n* = 1	5 years: OR 3.48 (2.50 to 4.86), 7	Based on seven studies, risk of severe disease increases with time from diagnosis
Location of disease	• Any location: 10,877; 4193 (32) • Colon only: 8584; 3500 (25) • Colonic any: 70,571; 2999 (23)		• Colonic only: surgery OR 0.42 (0.31 to 0.58), 11 • Colonic any: surgery OR 0.50 (0.36 to 0.69), 11	Disease confined to the colon is a predictor for less severe disease based on surgical outcome than having disease at any other location. Data synthesis only feasible for colonic only or colonic any

Biomarker	Overall number of participants; events expressed as minimum (studies)	Estimates reported[a]	Meta-analysis estimate (95% CI); *n* studies	Notes
Perianal disease	13,483; 5510 (24)	• OR, *n* = 13 • Adj OR, *n* = 1 • HR, *n* = 4 • Adj HR, *n* = 2 • *p*-value, *n* = 4	OR 1.84 (1.29 to 2.62); 13	10 studies report increased severe disease with presence of perianal disease
Smoking	11,475; 5097 (34)	• OR, *n* = 26 • Adj OR, *n* = 2 • HR, *n* = 1 • Adj HR, *n* = 1 • *p*-value, *n* = 4	OR 1.53 (1.30 to 1.79); 26	21 studies report increased severe disease with current smoking
Sex	14,489; 5350 (35)	• OR, *n* = 23 • Adj OR, *n* = 2 • HR, *n* = 5 • Adj HR, *n* = 1 • *p*-value, *n* = 4	OR 1.14 (0.98 to 1.31); 23	Sex has a non-significant association with severe disease. Approximately half of the studies favour men and half favour women for lower risk
Family history (Crohn's disease or IBD)	5687; 1413 (18)	• OR, *n* = 12 • Adj OR, *n* = 1 • HR, *n* = 1 • Adj HR, *n* = 1 • *p*-value, *n* = 3	OR 1.05 (0.81 to 1.36); 12	Family history has a non-significant association with severe disease. Five studies associated family history with increased risk while seven associated no family history with increased risk

Adj, adjusted; anti-CBir1, anti-flagellin antibody; ASCA, anti-*Saccharomyces cerevisiae* antibodies; HR, hazard ratio; *NOD2*, nucleotide-binding oligomerisation domain-containing protein 2.

a Hierarchy of estimates reported: OR, adj OR, HR and adj HR. For location, prediction groupings were restricted to colon only (disease located in colon only vs. disease not located in colon only) and colon any (disease present in colon as well as potentially in other locations vs. disease not present in colon). For duration, disease results were reported for 1, 3 and 5 years.

Notes

- Review question: to overview evidence for key prediction biomarkers for development of severe Crohn's disease.
- Patients/population: patients diagnosed with non-severe Crohn's disease.
- Role: biomarkers measured or available prior to development of severe disease.
- Biomarkers: serological, genetic or clinical biomarkers.
- Definition of severe disease: severe disease according to intestinal surgery, Beaugerie *et al.*,[18] Montreal behaviour,[19] NICE TA definition,[21] and Liege criteria.[20] Exclude relapse or disease flare.
- Studies: prospective cohort, retrospective case–control.
- Setting: mostly specialist IBD facilities, some specialist registries.
- ROB and applicability:
  - Three studies had a low ROB in all domains (Malmborg *et al.*,[59] Thia *et al.*,[89] Vernier-Massouille *et al.*[91]) and three had an unclear ROB (Lunney *et al.*,[58] Pittet *et al.*,[28] Sabate *et al.*[79]) A total of 65 studies were at a high ROB in at least one domain, mostly because of ROB in either flow and timing, or analysis domain. Thirty-one studies were rated with a high ROB in the flow and timing domain; 30 were rated as at a high ROB as the average time to event was not between 5 and 10 years. Forty studies were at a high ROB as fewer than three standard predictors were reported with significant results. Standard predictors were defined as those included in this overview.
  - Forty-five studies had an overall low concern for applicability, with 21 having an unclear rating and five having a high concern for applicability in at least one domain. High concerns for applicability were rated for four studies with composite outcomes defined in a slightly non-standard way and one study which enrolled only Indian patients with previous antituberculous therapy.

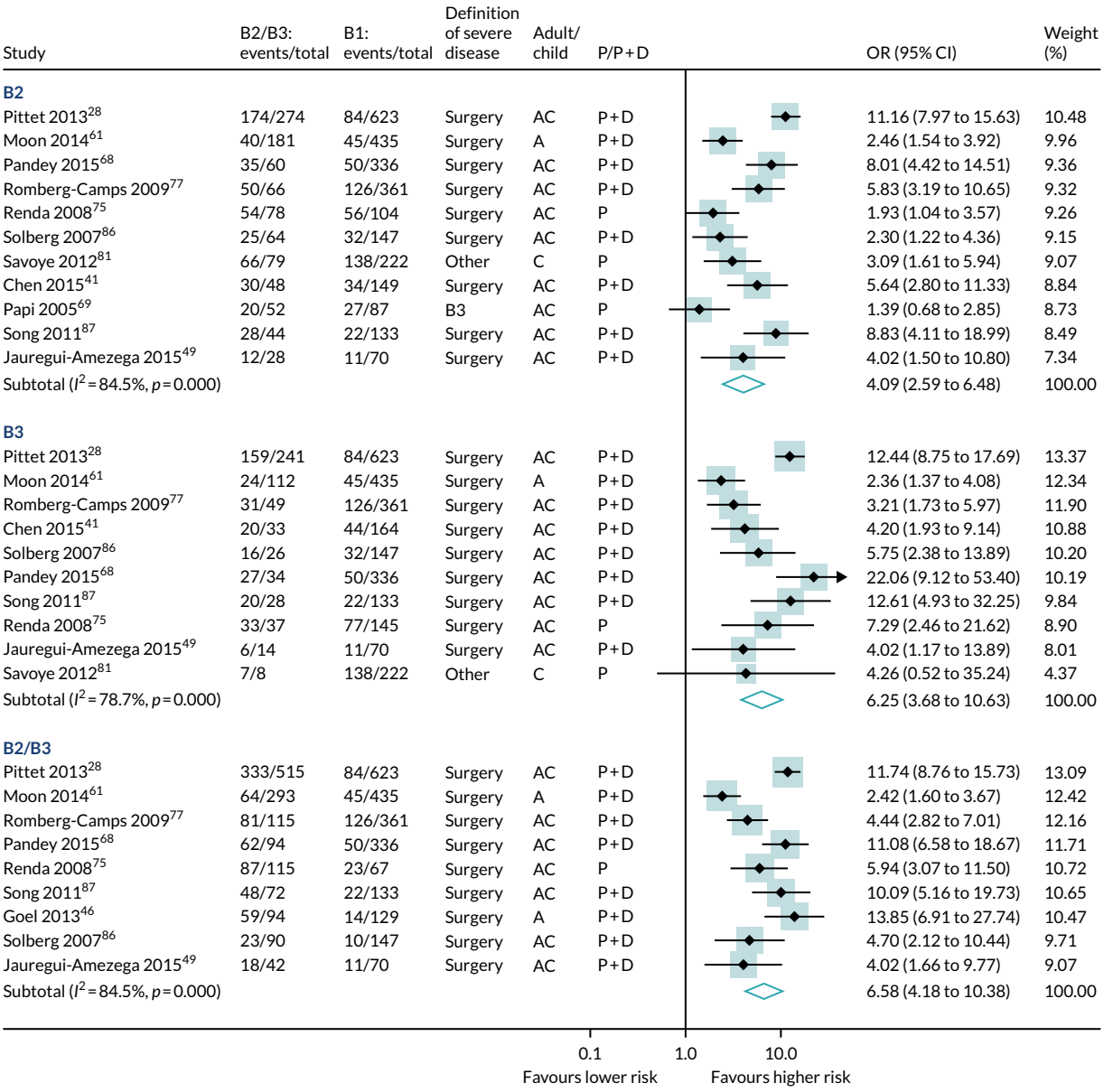

FIGURE 6 Forest plot of unadjusted ORs investigating Montreal disease behaviour as predictive of severe Crohn's disease. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

The participants' age at diagnosis was examined in 43 studies (19,623 participants, 7010 events). Most of the studies categorised age using the Montreal/Vienna thresholds, so data were greatest for three groups: aged < 17 years, aged 17–40 years and aged > 40 years. Overall, diagnosis at < 17 years of age was associated with a lower risk of severe Crohn's disease than other ages (see *Table 6* and *Figures 7–9*). Disease duration was examined in 14 studies (8690 participants, 1714 events). A meta-analysis found that increased duration of disease was associated with significant risk of severe disease at all durations examined (see *Table 6* and *Figures 7–9*).

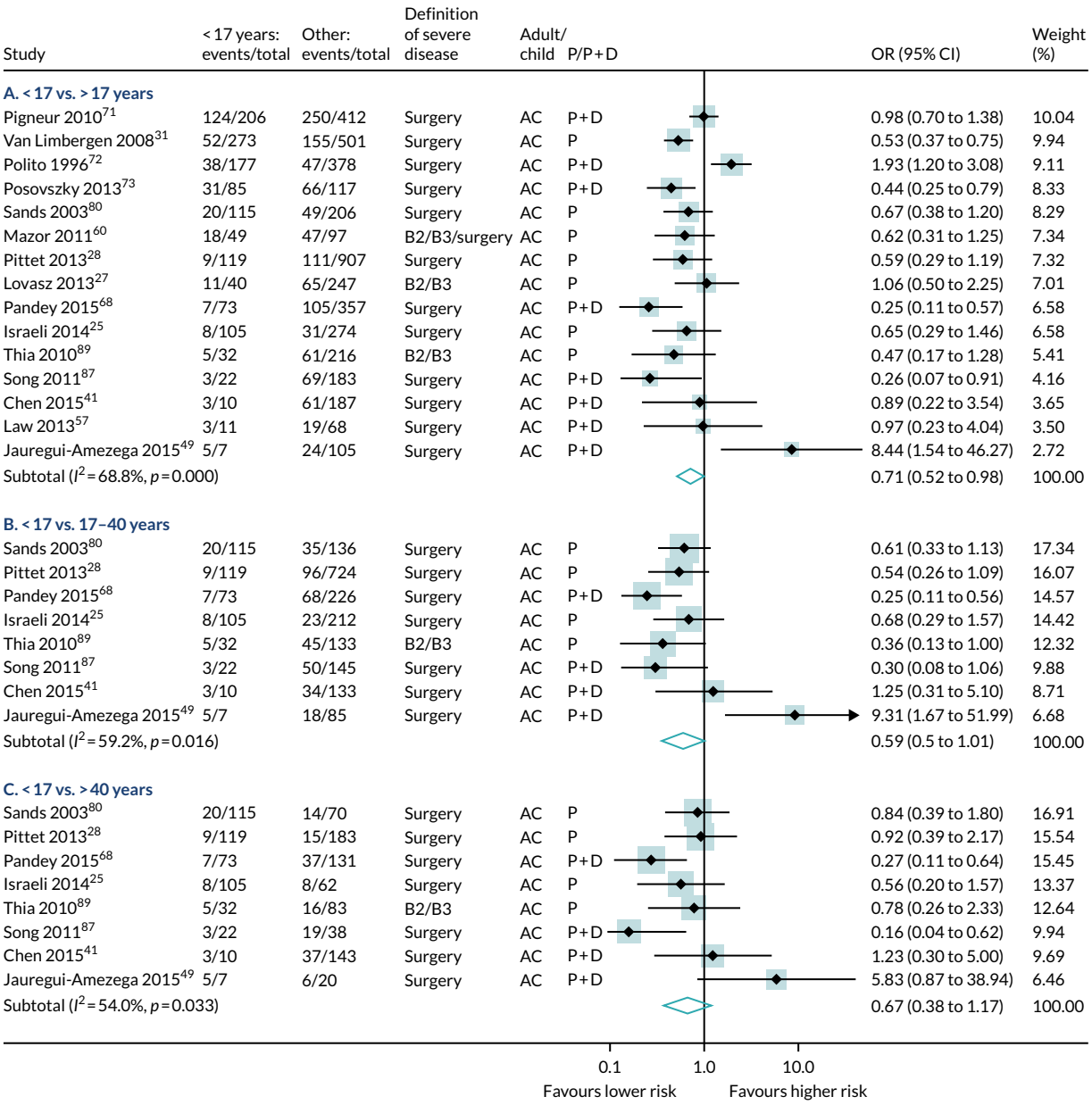

FIGURE 7 Forest plot of unadjusted ORs investigating age and disease duration as predictive markers for severe Crohn's disease: age at diagnosis < 17 years compared with > 17 years, 17–40 years and > 40 years. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

Disease location was examined in 32 studies (10,877 participants, 4193 events). Studies were diverse regarding the segments and/or segment combinations described. We could analyse 'colonic disease alone' and 'any colonic disease' versus other locations. Overall, colonic disease alone conferred significantly lower surgery risk than other locations (OR 0.42, 95% CI 0.31 to 0.58) (see *Table 6* and *Figure 10*).

Similarly, any colonic disease (23 studies, 7373 participants, 3086 events) predicted lower surgical or B2/B3 risk than no colonic disease (see *Table 6* and *Figure 11*).

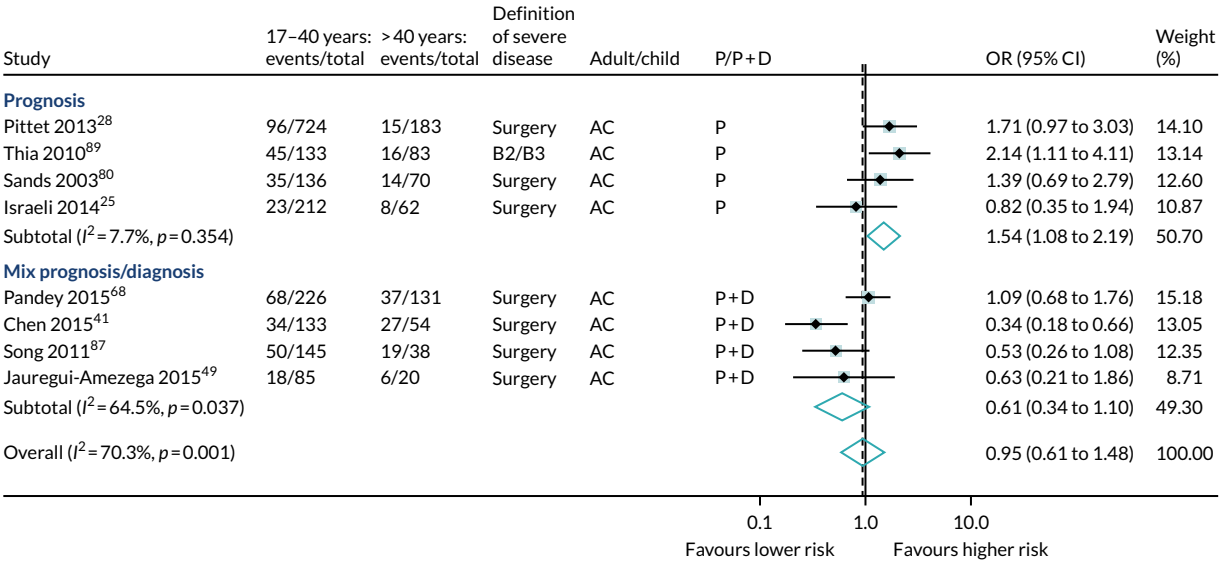

FIGURE 8 Forest plot of unadjusted ORs investigating age and disease duration as predictive markers for severe Crohn's disease: age at diagnosis 17–40 years compared with > 40 years. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

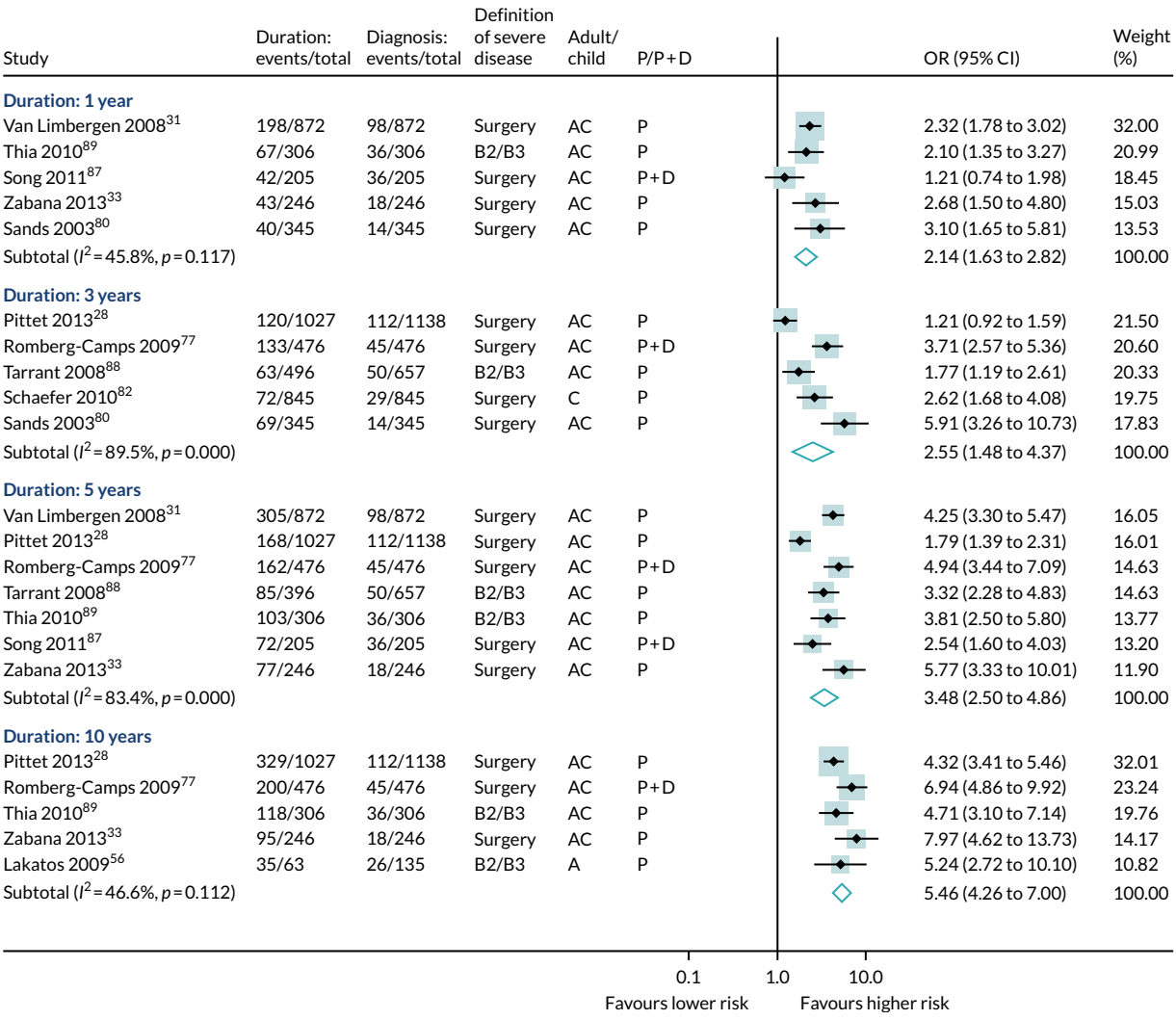

FIGURE 9 Forest plot of unadjusted ORs investigating age and disease duration as predictive markers for severe Crohn's disease: duration of disease, prognostic studies only. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

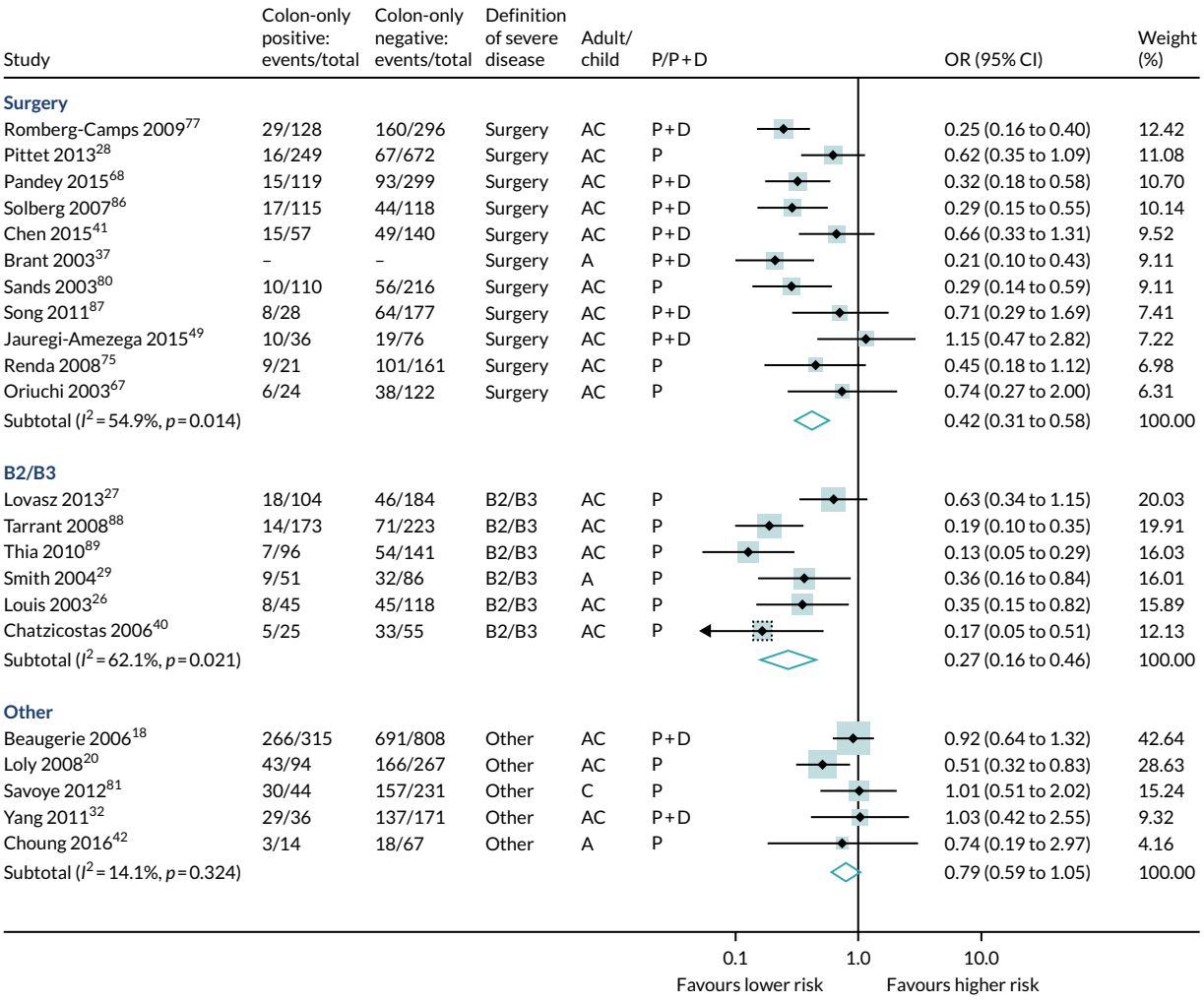

FIGURE 10 Forest plot of unadjusted ORs investigating disease location as predictive of severe Crohn's disease: colonic disease only. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

Perianal disease (24 studies, 13,483 participants, 5510 events) was associated with a significantly increased risk of subsequent severe disease overall (1.84 OR, 95% CI 1.29 to 2.62) (see *Table 6* and *Figure 12*).

A total of 34 studies reported an association of smoking with severe disease (11,475 participants, 5097 events); a meta-analysis of 26 studies found that current smoking increased the risk of severe Crohn's disease significantly (OR 1.53, 95% CI 1.30 to 1.79) (see *Table 6* and *Figure 13*).

Sex was examined in 35 studies (14,489 participants, 5350 events) and, overall, was not a significant predictor of severe Crohn's disease (see *Table 6* and *Figure 14*).

Family history was examined in 18 studies (5687 participants, 1413 events). A meta-analysis found no consistent direction and no significant association of family history and severe Crohn's disease (OR 1.05, 95% CI 0.81 to 1.36) (see *Table 6* and *Figure 15*).

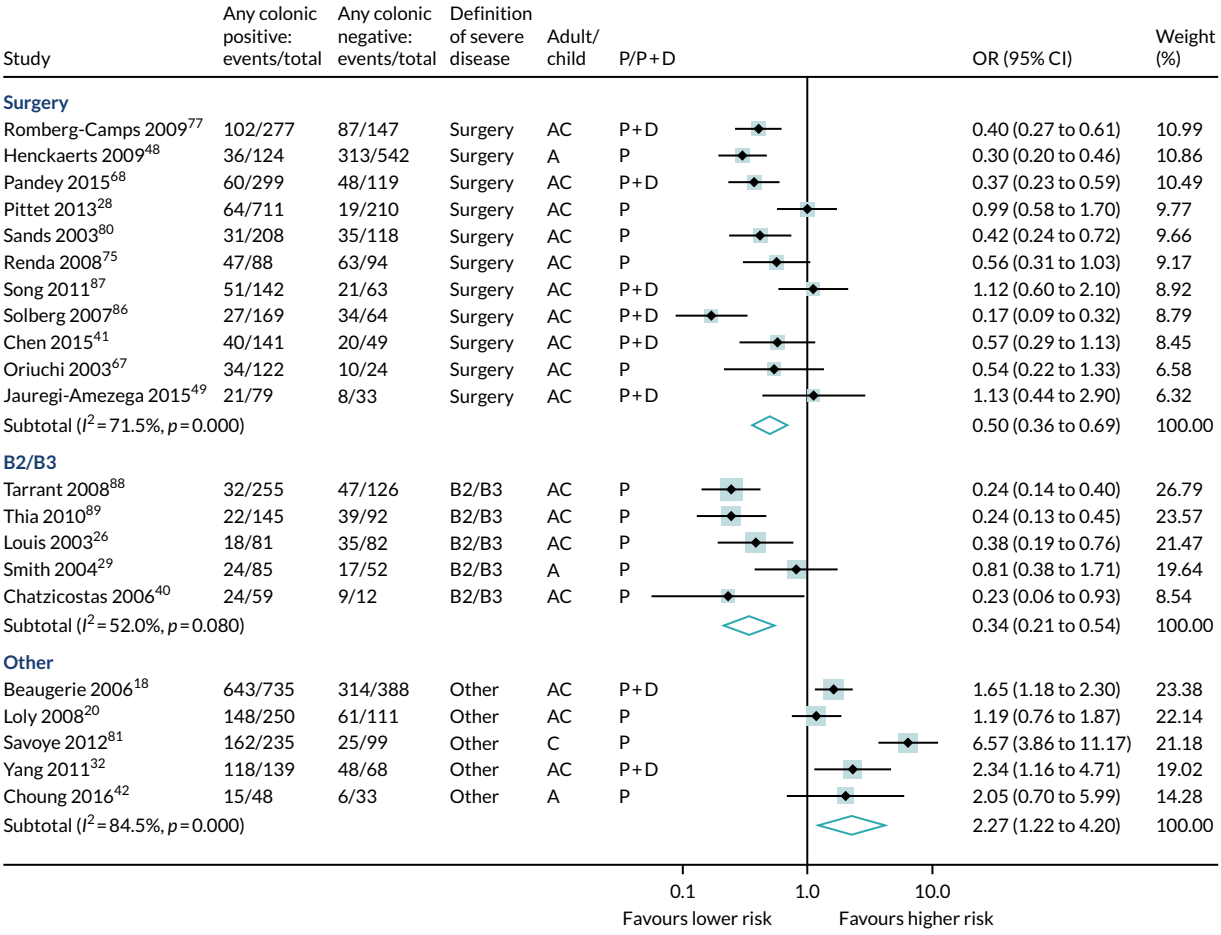

FIGURE 11 Forest plot of unadjusted ORs investigating disease location as predictive of severe Crohn's disease: any colonic involvement. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

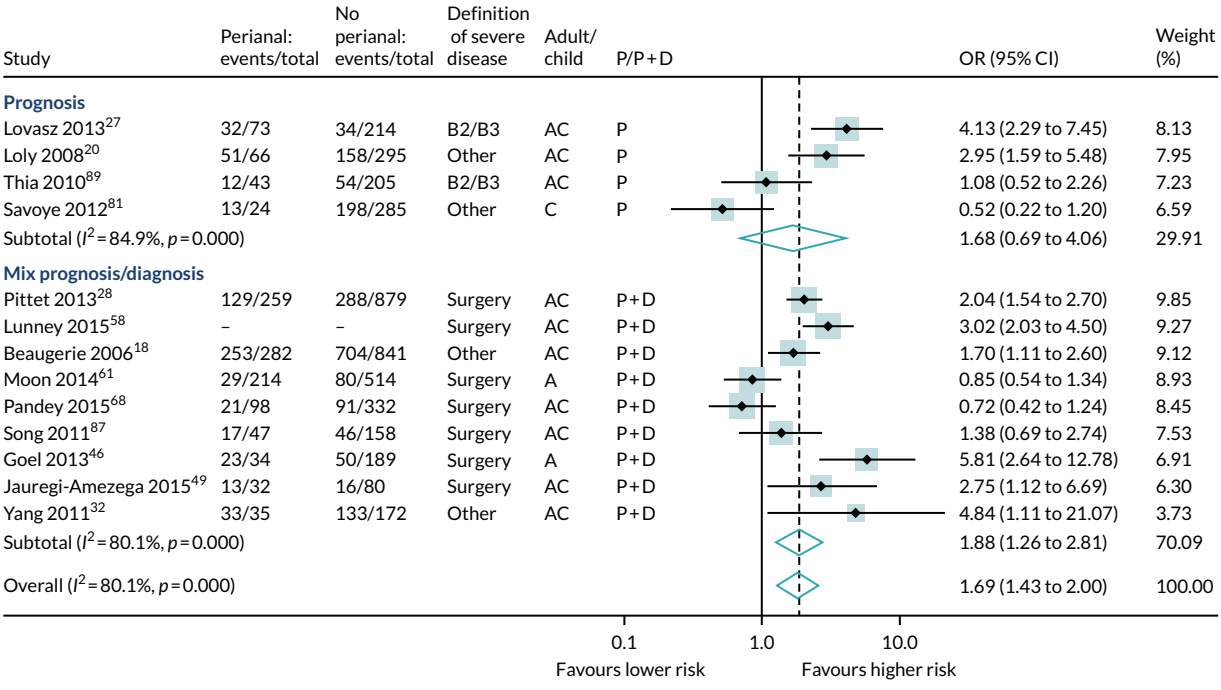

FIGURE 12 Forest plot of unadjusted ORs investigating disease location as predictive of severe Crohn's disease: perianal disease. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

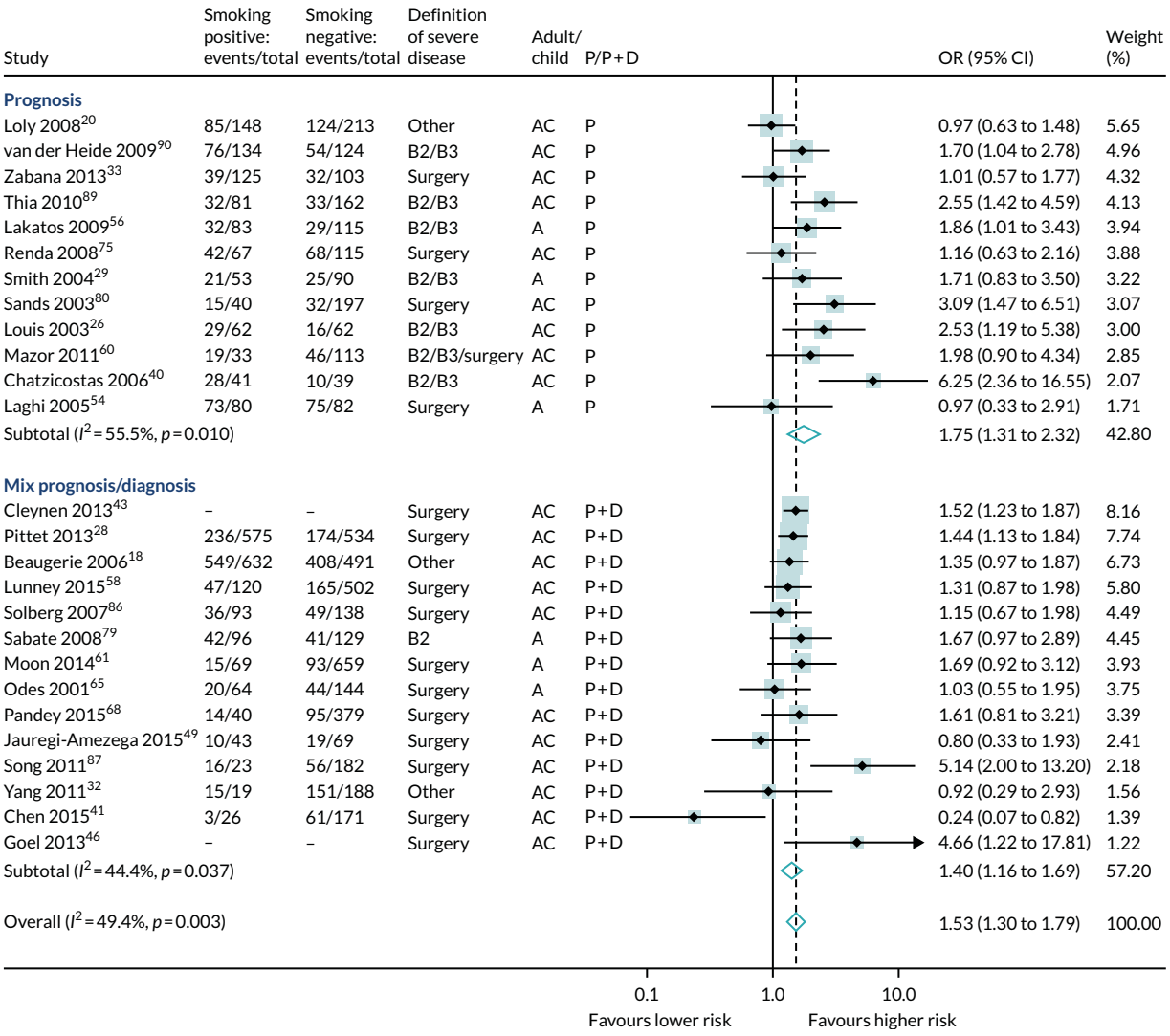

FIGURE 13 Forest plot of unadjusted ORs investigating smoking as a predictive marker for severe Crohn's disease. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

Meta-analysis of serological predictors

The following serological predictors had prognostic data available from fewer than five studies and, therefore, were not subject to meta-analysis: thrombocytosis, faecal calprotectin, anti-*Saccharomyces cerevisiae* antibodies (ASCA)-immunoglobulin (Ig)G, anti-CBir1, white blood cell (WBC), albumin, erythrocyte sedimentation rate (ESR), platelets, anaemia, CRP, haematocrit, ASCA-IgA, ferritin, anti-Fla2, anti-FlaX, anti-L IgA, anti-C IgA, anti-*Saccharomyces chitobioside* antibody (ACCA)-IgA, anti-*Saccharomyces laminaribioside* antibody (ALCA)-IgG, anti-*Saccharomyces mannobioside* antibody (AMCA)-IgG and anti-I2.

Three serological markers (ASCA, anti-CBir1 and CRP) from 13 studies were meta-analysed. ASCA and anti-CBir1 showed potential prognostic association; ASCA-positive patients had significantly increased odds of developing severe disease (OR 2.29, 95% CI 1.31 to 3.99; six studies) (see *Table 6* and *Figure 16*).

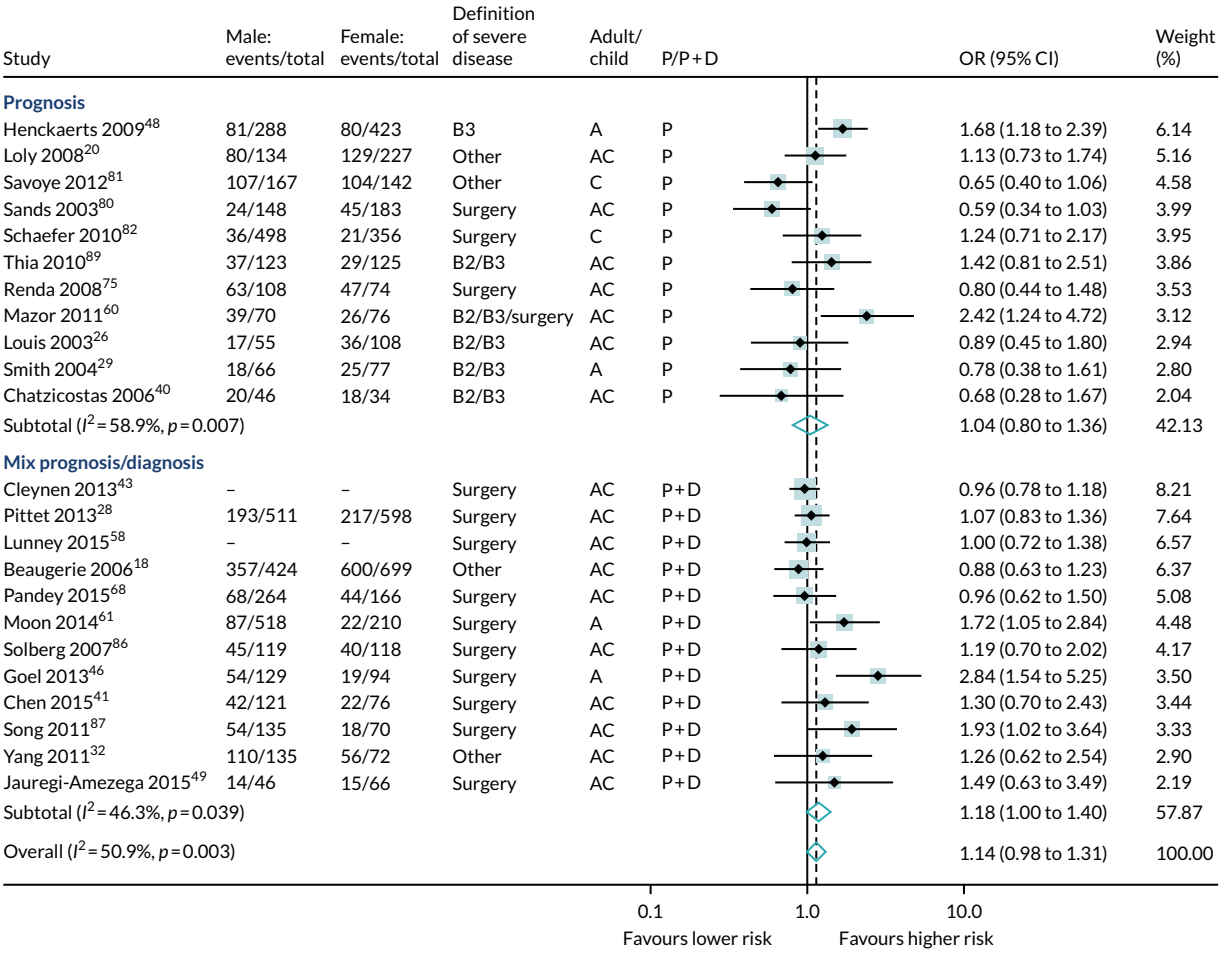

FIGURE 14 Forest plot of unadjusted ORs investigating sex as a predictive marker for severe Crohn's disease. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

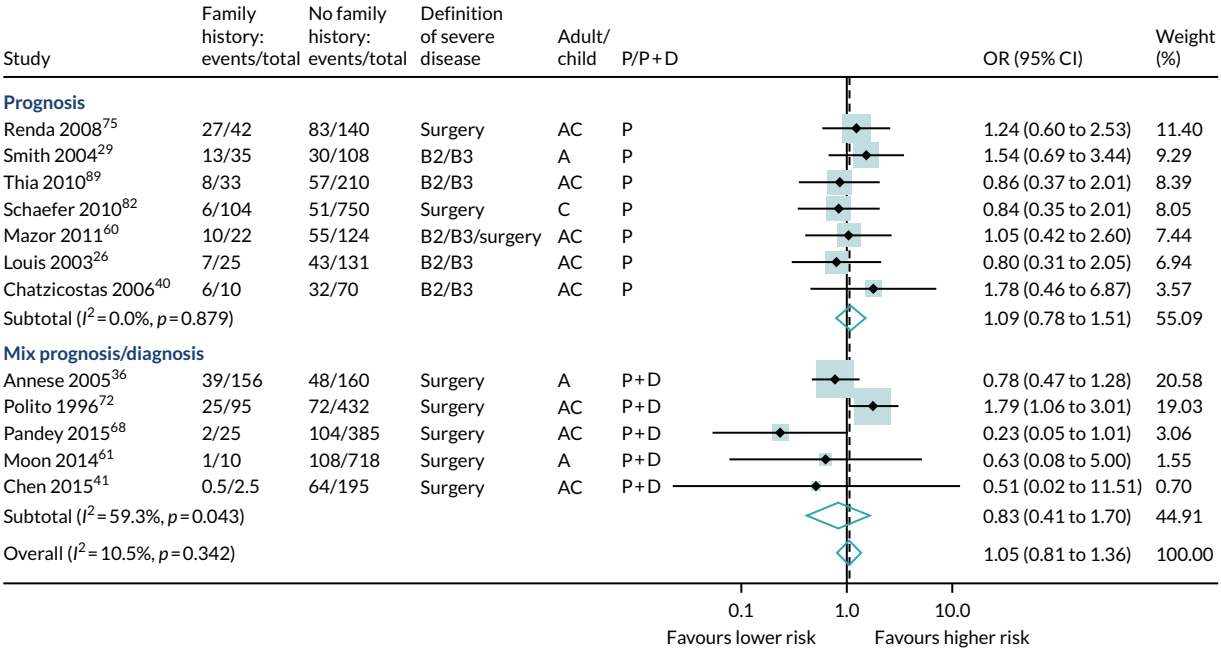

FIGURE 15 Forest plot of unadjusted ORs investigating family history as a predictive marker for severe Crohn's disease. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

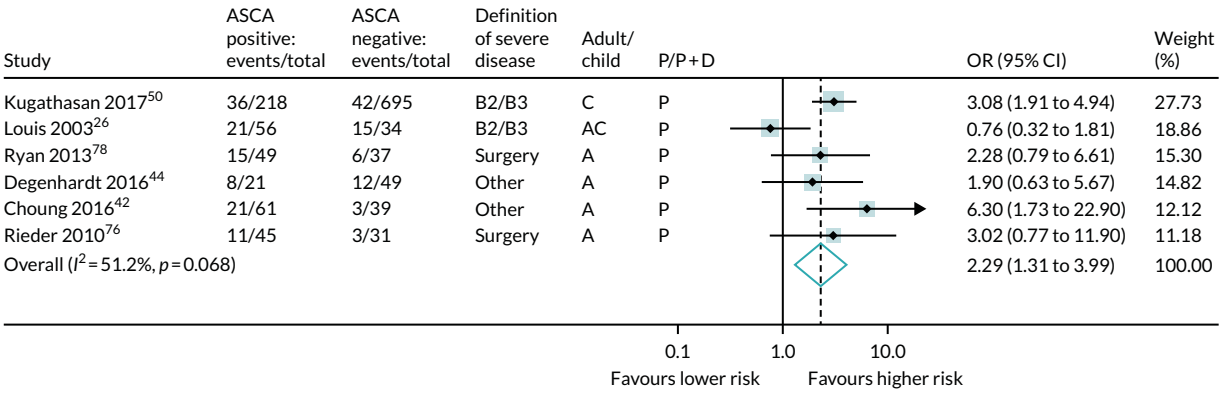

FIGURE 16 Forest plot of unadjusted ORs investigating serological markers as predictors of severe Crohn's disease: ASCA. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

Anti-CBir1 data were identified from five studies; meta-analysis from ORs did not reach significance (see *Table 6* and *Figure 17*), but additional evidence from hazard ratios indicated a significant association between anti-CBir1 and severe Crohn's disease (*Table 7*).

For CRP, data were identified from only three studies (the expert panel requested that CRP was included) and the results found no significant predictive association of CRP and severe Crohn's disease (see *Table 6* and *Figure 18*).

Meta-analysis of genetic predictors

The following genetic predictors had prognostic data available from fewer than five studies and, therefore, were not subject to meta-analysis: *LOC441108*, *TNFSF15*, *5p13.1*, *NCF4*, *CX3CR1*, *JAK2*, *SBNO2*, *ZPBP*, *PTGER4*, *PUS10*, *PRDM1*, *C13ORF31*, *SLC22A23*, *TAB2/MAP3K7IP2*, *PTPN22*, *ICOSLG*, *STAT3*, *PTPN2*, *NKX2-3*, *POU2E1*, *U10*, *U7*, *AK097548*, *CDKAL1*, *HERC2*, *ATG4A*, *NALP3*, *IL21*, *CARD8*, nucleotide-binding oligomerisation domain-containing protein 2 (*NOD2*) – all 3 versus 0, *TLR4 D299G*, *FOXO3a*, *IBD5*, *DLG5*, *PAI-1*, *SMAD3*, *MMP*, *TIMP*, *ATG2A*, *FNBP1L* and *ATG4D*.

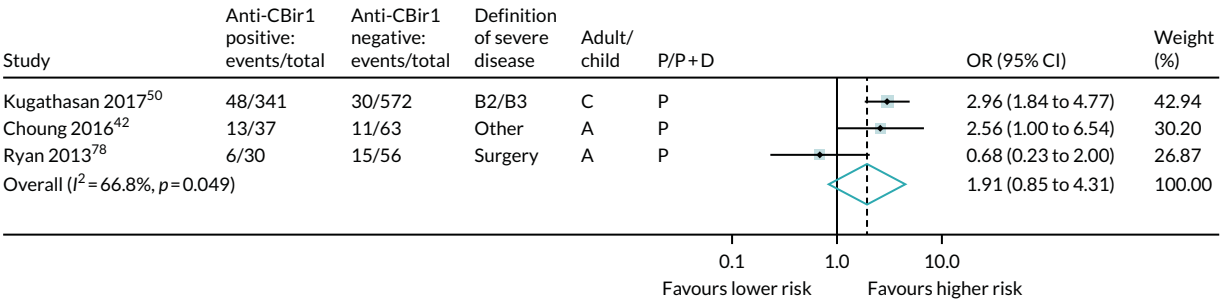

FIGURE 17 Forest plot of unadjusted ORs investigating serological markers as predictors of severe Crohn's disease: anti-CBir1. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

TABLE 7 Summary of the data not presented in forest plots

Predictor	Study (first author and year)	Definition of serious disease	Number of participants	Number of events	Outcome	Significant	Point estimate (95% CI)
ASCA	Annese 2005[36]	B2	316	NR	*p*-value	Yes	0.046
	Dubinsky 2008[45]	Surgery	592	61	HR	Yes	3.2 (1.1 to 9.5)
	Loly 2008[20]	Other	73	NR	*p*-value	No	NS
	Siegel 2016[85]	B2/B3/ surgery	243	142	HR	Yes	1.42 (1.24 to 1.63)
CBir-1	Dubinsky 2008[45]	B2/B3	536	37	HR	Yes	2.5 (1.2 to 5.2)
	Siegel 2016[85]	B2/B3/ surgery	243	142	HR	Yes	1.47 (1.24 to 1.75)
CRP	All studies in MA						
NOD2	Shaoul 2009[83]	Surgery	119	38	*p*-value	No	NS
Disease behaviour (B3)	Vester-Andersen 2014[92]	Surgery	213	49	*p*-value	No	NR
	Park 2013[70]	Surgery	1403	471	Adj HR	Yes	5.67 (4.51 to 7.11)
Disease behaviour (NR)	Brant 2003[37]	Surgery	257	183	*p*-value	NR	NR
Disease behaviour (B2/B3)	Nunes 2013[64]	Surgery	3118	1269	Adj HR	Yes	4.42 (3.87 to 5)
Age at diagnosis	Annese 2005[36]	Surgery	316	87	Adj OR	Yes	1.37 (1.05 to 1.79)
Duration of disease	Renda 2008[75]	Surgery	182	110	HR	No	0.9 (0.9 to 1.02) at 1.5 years
	Goel 2013[46]	B2/B3	223	93	*p*-value	No	> 0.3 at 6 years
Location: colonic only	Malmborg 2015[59]	B2/B3/ surgery	161	25	HR	No	0.72 (0.33 to 1.59)
	Aldhous 2007[34]	Surgery	251	113	Adj HR	Yes	0.27 (0.16 to 0.45)
	Park 2013[70]	Surgery	1403	471	Adj HR	Yes	0.36 (0.2 to 0.64)
Location: any colonic	Papi 2005[69]	B3	139	47	Adj HR	No	0.7 (0.3 to 1.6)
	Annese 2005[36]	Surgery	316	87	*p*-value	No	NS
Perianal	Annese 2005[36]	Surgery	316	87	*p*-value	No	NS
	Brant 2003[37]	Surgery	257	183	*p*-value	No	NS
	Chen 2015[41]	Surgery	197	64	HR	No	0.68 (0.32 to 1.42)
	Law 2013[57]	Other	79	34	*p*-value	No	NS

TABLE 7 Summary of the data not presented in forest plots (*continued*)

Predictor	Study (first author and year)	Definition of serious disease	Number of participants	Number of events	Outcome	Significant	Point estimate (95% CI)
	Nasir 2013[62]	Surgery	503	240	Adj OR	Yes	2.84 (1.83 to 4.38)
	Nunes 2013[64]	Surgery	3201	1313	Adj HR	Yes	1.32 (1.17 to 1.5)
	Park 2013[70]	Surgery	1403	471	Adj HR	No	1.09 (0.91 to 1.32)
	Ryan 2013[78]	Surgery	182	77	*p*-value	No	0.06
	Siegel 2016[85]	B2/B3/ surgery	243	142	HR	No	0.86 (0.54 to 1.37)
	Tarrant 2008[88]	B2/B3	715	189	HR	Yes	1.62 (1.28 to 2.05)
	Vernier-Massouille 2008[91]	Surgery	394	176	HR	No	0.94 (0.53 to 1.65)
Smoking	Lovasz 2013[27]	B2/B3	287	110	HR	No	1.48 (0.96 to 2.37)
	Law 2013[57]	Other	79	34	Adj HR	Yes	4.68 (1.03 to 4.09)[a]
	Brant 2003[37]	Surgery	257	183	*p*-value	No	NS
	Goel 2013[46]	Surgery	223	73	*p*-value	No	> 0.3
	Ryan 2013[78]	Surgery	182	77	*p*-value	No	0.05
	Vester-Andersen 2014[92]	Surgery	213	49	*p*-value	No	NS
	Annese 2005[36]	Surgery	316	87	Adj OR	Yes	1.42 (1.06 to 1.88)
	Papi 2005[69]	B3	139	47	Adj OR	No	1.2 (0.5 to 2.6)
Sex	Nasir 2013[63]	Surgery	503	240	Adj OR	No	1.16 (0.77 to 1.74)
	Papi 2005[69]	B3	139	47	Adj OR	No	1.67 (0.33 to 2.17)
	Gupta 2006[47]	Surgery	989	128	HR	No	1.42 (1.00 to 2.01)
	Malmborg 2015[59]	B2/B3/ surgery	161	25	HR	No	0.59 (0.31 to 1.15)
	Siegel 2011[84]	B2/B3	579	67	HR	No	0.55 (0.3 to 1.01)
	Charpentier 2014[39]	Surgery	367	103	HR	No	1.3 (0.8 to 1.9)
	Vernier-Massouille 2008[91]	Surgery	394	176	HR	No	0.96 (0.71 to 1.3)
	Aldhous 2007[34]	B2/B3	274	105	Adj HR	No	0.89 (0.6 to 1.3)
	Annese 2005[36]	Surgery	316	87	*p*-value	No	NS

continued

TABLE 7 Summary of the data not presented in forest plots (*continued*)

Predictor	Study (first author and year)	Definition of serious disease	Number of participants	Number of events	Outcome	Significant	Point estimate (95% CI)
	Brant 2003[37]	Surgery	257	183	*p*-value	NR	NR
	Law 2013[57]	Other	79	34	*p*-value	No	NS
	Ryan 2013[78]	Surgery	182	77	*p*-value	No	NS
Family history	Papi 2005[69]	B3	139	47	Adj OR	No	2 (0.5 to 7.6)
	Malmborg 2015[59]	B2/B3/ surgery	161	17	HR	No	0.21 (0.03 to 1.56)
	Aldhous 2007[34]	Surgery	251	113	Adj HR	No	1.06 (0.65 to 1.73)
	Brant 2003[37]	Surgery	257	183	*p*-value	No	NS
	Ryan 2013[78]	Surgery	182	77	*p*-value	No	NS
	Tarrant 2008[88]	B2/B3	715	85	*p*-value	No	NS

Adj, adjusted; HR, hazard ratio; MA, meta-analysis; NR, not reported; NS, not significant.
a 95% CI is as reported in the original publication.

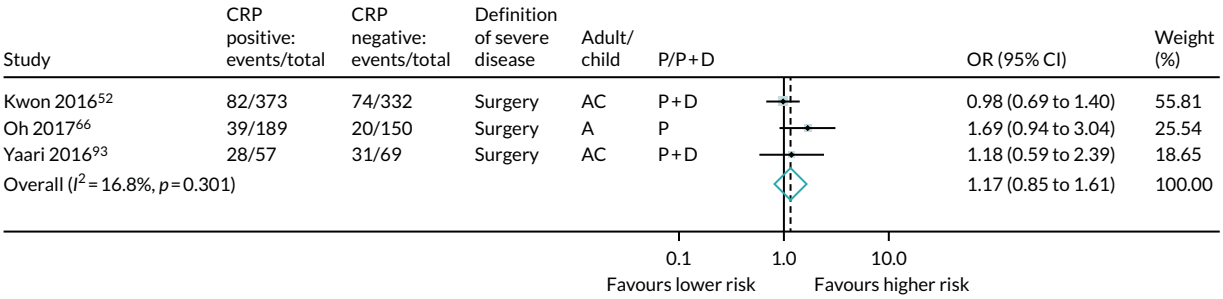

FIGURE 18 Forest plot of unadjusted ORs investigating serological markers as predictors of severe Crohn's disease: CRP. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

Of the genetic markers, results for *NOD2* in at least one variant were reported in 17 studies, although one study reported only *p*-values and was excluded from meta-analysis.[83] Meta-analysis of 16 studies (5407 participants, 2645 events) suggested higher risk of severe Crohn's disease with a *NOD2* variant gene overall (OR 1.69, 95% CI 1.43 to 2.00); studies were a mix of prognosis and prognosis/diagnosis (see *Table 6* and *Figure 19*).

Identification of existing systematic reviews

During this review, we identified seven previous systematic reviews that investigated the association of mostly serological and some genetic biomarkers with severe Crohn's disease.[94–100] Three of these reviews[95,99,100] did not separate primary studies of diagnosis and prognosis. One review[95] identified two studies of predictive biomarkers, one of which[76] was also identified as the only prognostic study by a second review.[96] The remaining systematic review[101] included three biomarker prediction studies, only one of which met our inclusion criteria.

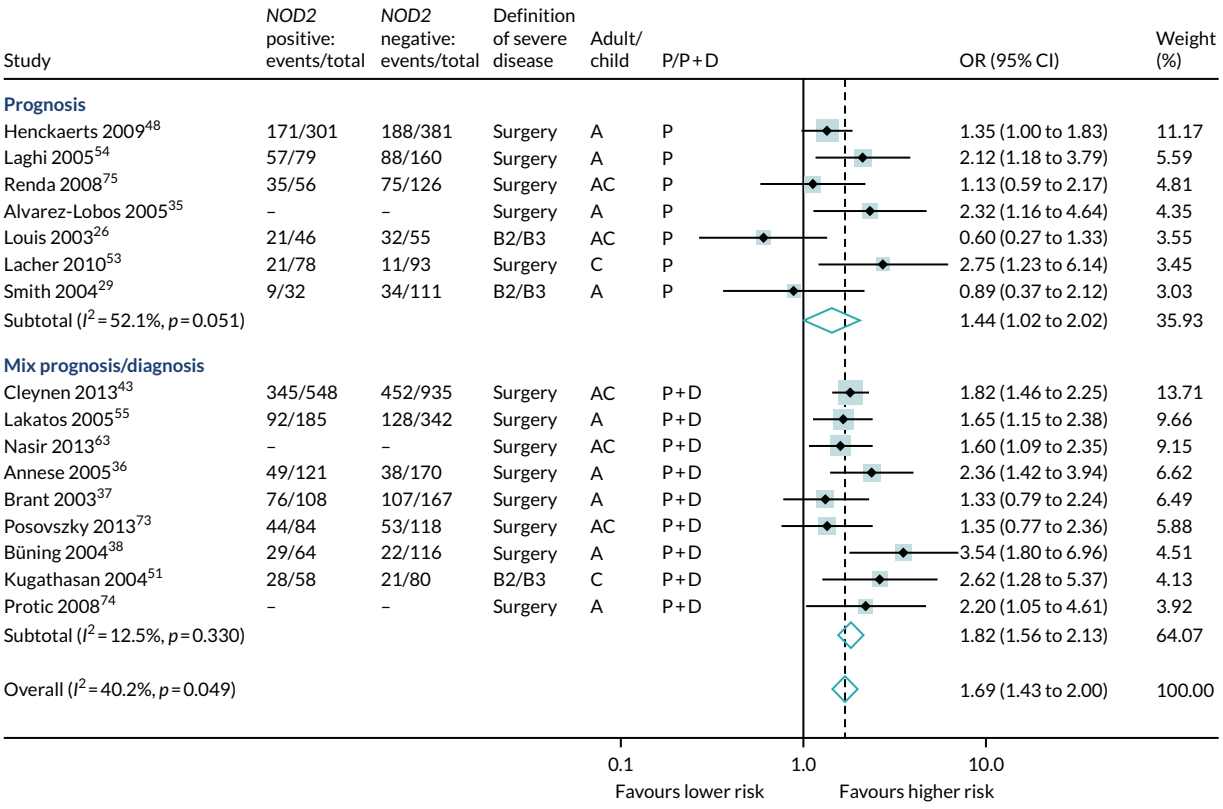

FIGURE 19 Forest plot of unadjusted ORs investigating *NOD2* (any variant) as a predictor of severe Crohn's disease. A, adult; AC, both adults and children; C, child; P, predictive effect only; P + D, predictive and diagnostic effect combined.

Search update: August 2020

To obtain an estimate of new data subsequent to our original search, we repeated the search at the time of revising this monograph (August 2020). The search period was extended from 2016 to 17 August 2020, inclusive. The search string identified 4005 indexed studies from PubMed and 6878 studies from EMBASE. The researcher who performed the original search (Darren Boone) examined the abstracts of all of these studies to identify studies of biomarkers with potentially prognostic data. Ultimately, we identified 87 papers, seven of which were identified by our updated search for serological markers that extended to 1 January 2018. That is, at the time of writing there were potentially 80 additional papers that contained prognostic data relevant to our review question. All of these papers were identified by the PubMed search; once duplicates had been removed, the EMBASE search contributed no potentially relevant material. We identified no new biomarker that would satisfy our a priori threshold for inclusion of reporting in five or more individual papers. Our original search retained 29% of those papers subject to full-text review. A similar proportion applied here would suggest that around 23 of these 80 papers would be suitable for inclusion, the large majority of which examine phenotype and/or age and/or smoking. We are, therefore, as confident as we can be that at the time of writing there are insufficient indexed data to alter our conclusions relating to genetic and serological biomarkers, and that our meta-analytical data relating to clinical factors are likely to stand unchanged. *Table 8* details the additional potentially relevant research that was identified, which has been split by biomarker(s) investigated.

TABLE 8 Summary of the potentially relevant research identified by an updated search performed in August 2020

Study (first author and year)	Title	Clinical biomarker(s)	Serological biomarker(s)	Genetic biomarker(s)
Aaltonen 2019[102]	Risk factors for proctectomy in consecutive Crohn's colitis surgical patients in a reference colorectal centre	Duration, gender and perianal disease		
Aggarwal 2017[103]	Role of capsule endoscopy and fecal biomarkers in small-bowel Crohn's disease to assess remission and predict relapse	CDAI	Calprotectin	
Alexakis 2018[104]	Smoking status at diagnosis and subsequent smoking cessation: associations with corticosteroid use and intestinal resection in Crohn's disease	Smoking		
Arieira 2018[105]	Clinical course in Crohn's disease: factors associated with behaviour change and surgery	Age, phenotype and smoking		
Arora 2018[106]	Effect of oral tobacco use and smoking on outcomes of Crohn's disease in India	Sex and smoking		
Arora 2018[107]	Colonic Crohn's disease is associated with less aggressive disease course than ileal or ileocolonic disease	Phenotype		
Assa 2017[108]	Perianal pediatric Crohn disease is associated with a distinct phenotype and greater inflammatory burden	Phenotype and perianal disease		
Assa 2018[109]	The long-term predictive properties of the Paris classification in paediatric inflammatory bowel disease patients	Phenotype	ASCA	
Birimberg-Schwartz 2016[110]	pANCA and ASCA in children with IBD-unclassified, Crohn's colitis, and ulcerative colitis-A longitudinal report from the IBD Porto Group of ESPGHAN		pANCA and ASCA	
Bossuyt 2018[111]	Risk stratification for surgery in stricturing ileal Crohn's disease: the BACARDI risk model	Phenotype	CRP	*NOD2*
Brückner 2018[112]	Incidence and risk factors for perianal disease in pediatric Crohn disease patients followed in CEDATA-GPGE registry	Sex, family history, EIMs and phenotype		
Buisson 2019[113]	Faecal calprotectin is a very reliable tool to predict and monitor the risk of relapse after therapeutic de-escalation in patients with inflammatory bowel diseases		Calprotectin	
Burisch 2019[114]	Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study	Phenotype		
Chaparro 2019[115]	Differences between childhood- and adulthood-onset inflammatory bowel disease: the CAROUSEL study from GETECCU	Age at onset, sex, EIMs, FHx and smoking		

TABLE 8 Summary of the potentially relevant research identified by an updated search performed in August 2020 (*continued*)

Study (first author and year)	Title	Clinical biomarker(s)	Serological biomarker(s)	Genetic biomarker(s)
Chaudhry 2017[116]	A fixed stricture on routine cross-sectional imaging predicts disease-related complications and adverse outcomes in patients with Crohn's disease	Phenotype and smoking	Haemoglobin and CRP	
Chen 2017[117]	Performance of risk prediction for inflammatory bowel disease based on genotyping platform and genomic risk score method	Age, age at diagnosis and phenotype		GWAS
Chhaya 2016[118]	Emerging trends and risk factors for perianal surgery in Crohn's disease: a 20-year national population-based cohort study	Age, sex and location		
Chun 2018[119]	Association of perianal fistulas with clinical features and prognosis of Crohn's disease in Korea: results from the CONNECT study	Phenotype, age and sex		
de Barros 2017[120]	Evolution of clinical behavior in Crohn's disease: factors associated with complicated disease and surgery	Age, smoking, phenotype and age at diagnosis		
Dias 2017[121]	The risk of disabling, surgery and reoperation in Crohn's disease – a decision tree-based approach to prognosis	Phenotype		
Dias 2017[122]	Development and validation of risk matrices for Crohn's disease outcomes in patients who underwent early therapeutic interventions	Age at diagnosis, perianal disease and phenotype		
Diederen 2017[123]	Raised faecal calprotectin is associated with subsequent symptomatic relapse, in children and adolescents with inflammatory bowel disease in clinical remission	PCDAI	CRP and calprotectin	
Dong 2019[124]	A novel surgical predictive model for Chinese Crohn's disease patients	Phenotype	CRP, WBCs and PLts	
Foster 2019[125]	Consecutive faecal calprotectin measurements for predicting relapse in paediatric Crohn's disease patients	PCDAI	CRP and ESR	
Fumery 2016[126]	Natural history of Crohn's disease in elderly patients diagnosed over the age of 70 years: a population-based study	Phenotype and EIMs		
Fumery 2019[127]	Long-term outcome of paediatric-onset Crohn's disease: a population-based cohort study	Phenotype		
Gasparetto 2016[128]	Clinical course and outcomes of diagnosing Inflammatory Bowel Disease in children 10 years and under: retrospective cohort study from two tertiary centres in the United Kingdom and in Italy	Age at onset, EIMs and phenotype		

continued

TABLE 8 Summary of the potentially relevant research identified by an updated search performed in August 2020 (*continued*)

Study (first author and year)	Title	Clinical biomarker(s)	Serological biomarker(s)	Genetic biomarker(s)
Guizzetti 2018[129]	Development of clinical prediction models for surgery and complications in Crohn's disease	Age, gender, disease location and HBI		
Herman 2017[130]	The characteristics and long-term outcomes of pediatric Crohn's disease patients with perianal disease	Age, sex and HBI	Laboratory data	
Herzog 2018[131]	Age at disease onset of inflammatory bowel disease is associated with later extraintestinal manifestations and complications	Phenotype, sex and smoking		
Hou 2016[132]	Characteristics and behavior of elderly-onset inflammatory bowel disease: a multi-center US study	Age at onset		
Huguet 2018[133]	Inflammatory bowel disease in patients over the age of 70 years. Does the disease duration influence its behavior?	Age		
Hwang 2017[134]	Influence of age at diagnosis on the clinical characteristics of Crohn's disease in Korea: results from the CONNECT study	Age at onset		
Jeuring 2017[135]	Improvements in the long-term outcome of Crohn's disease over the past two decades and the relation to changes in medical management: results from the population-based IBDSL cohort	Phenotype		
Jeuring 2016[136]	Epidemiology and long-term outcome of inflammatory bowel disease diagnosed at elderly age-an increasing distinct entity?	Age and phenotype		
Jones 2019[137]	Faecal calprotectin and magnetic resonance enterography in ileal Crohn's disease: correlations between disease activity and long-term follow-up	Age and MRI	Calprotectin	
Kaur 2016[138]	Perianal Crohn's disease is associated with distal colonic disease, stricturing disease behaviour, IBD-associated serologies and genetic variation in the JAK-STAT pathway	Phenotype and FHx	ASCA and OmpC	Multiple Loci
Kayar 2019[139]	Risk factors associated with progression to intestinal complications of Crohn disease	Smoking, EIMs and phenotype		
Kim 2017[140]	Clinical characteristics and long-term outcomes of paediatric Crohn's Disease: a single-centre experience	Age, sex, FHx and phenotype		
Kim 2017[141]	Incidence of and risk factors for free bowel perforation in patients with Crohn's disease	Sex, age at diagnosis and phenotype		
Kim 2018[142]	The clinical characteristics and prognosis of Crohn's disease in Korean patients showing proximal small bowel involvement: results from the CONNECT study	Phenotype		

TABLE 8 Summary of the potentially relevant research identified by an updated search performed in August 2020 (*continued*)

Study (first author and year)	Title	Clinical biomarker(s)	Serological biomarker(s)	Genetic biomarker(s)
Kostas 2017[143]	Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease		CRP and calprotectin	
Kühn 2018[144]	[Risk factors for early surgery and surgical complications in Crohn's disease]	Age at onset and phenotype	CRP and albumin	
Kunovsky 2019[145]	The role of the *NOD2/CARD15* gene in surgical treatment prediction in patients with Crohn's disease			*NOD2*
Kupka 2018[146]	Crohn's disease – genetic factors and progress of the disease	Phenotype		*NOD2*
Kwapisz 2017[147]	The utility of fecal calprotectin in predicting the need for escalation of therapy in inflammatory bowel disease		Calprotectin	
Levine 2020[148]	Complicated disease and response to initial therapy predicts early surgery in paediatric Crohn's disease: results from the Porto Group GROWTH study	Phenotype and PCDAI	Anti-OmpC	
Liu 2018[149]	Lémann index at diagnosis predicts the risk of early surgery in Crohn's disease	Lémann index at diagnosis and phenotype		
Mańkowska-Wierzbicka 2016[150]	C-reactive protein as a diagnostic and prognostic factor in inflammatory bowel diseases	Age	CRP	
Mañosa 2018[151]	Phenotype and natural history of elderly onset inflammatory bowel disease: a multicentre, case–control study	Age at onset and phenotype		
Mosli 2018[152]	Risk stratification of patients with Crohn's disease: a retrospective analysis of clinical decision-making and its impact on long-term outcome	Age, smoking, Montreal and age at diagnosis		
Müller 2016[153]	Baseline characteristics and disease phenotype in inflammatory bowel disease	PCDAI, age and phenotype	CRP	
Naganuma 2016[154]	Endoscopic severity predicts long-term prognosis in Crohn's disease patients with clinical remission	Phenotype	CRP	
Nahon 2016[155]	Diagnostic delay is associated with a greater risk of early surgery in a French cohort of Crohn's disease patients	Age at onset and phenotype		
Ng 2016[156]	Early course of inflammatory bowel disease in a population-based inception cohort study from 8 countries in Asia and Australia	Phenotype		
Nguyen 2017[157]	Risk of surgery and mortality in elderly-onset inflammatory bowel disease: a population-based cohort study	Age at onset and phenotype		
Ouaz 2016[158]	Changes of Crohn's disease phenotype over time	Phenotype, smoking, age and sex		

continued

TABLE 8 Summary of the potentially relevant research identified by an updated search performed in August 2020 (*continued*)

Study (first author and year)	Title	Clinical biomarker(s)	Serological biomarker(s)	Genetic biomarker(s)
Pallotta 2018[159]	A risk score system to timely manage treatment in Crohn's disease: a cohort study	Age, sex, phenotype, CDAI and age at diagnosis	CRP	
Park 2019[160]	Update on the natural course of fistulizing perianal Crohn's disease in a population-based cohort			
Park 2017[161]	Development of a novel predictive model for the clinical course of Crohn's disease: results from the CONNECT study	Age and phenotype		
Parker 2016[162]	Radiologic predictors of surgery in newly diagnosed pediatric Crohn disease patients	Phenotype		
Pernat Drobež 2018[163]	DNA polymorphisms predict time to progression from uncomplicated to complicated Crohn's disease			Multiple loci
Rinawi 2016[164]	Evolution of disease phenotype in pediatric-onset Crohn's disease after more than 10 years follow up – cohort study	Phenotype		
Rispo 2018[165]	Combined endoscopic/sonographic-based risk matrix model for predicting one-year risk of surgery: a prospective observational study of a tertiary centre severe/refractory Crohn's disease cohort	Phenotype		
Rönnblom 2017[166]	Clinical course of Crohn's disease during the first 5 years. Results from a population-based cohort in Sweden (ICURE) diagnosed 2005–2009	Phenotype		
Saad 2016[167]	Age of diagnosis is associated with disease presentation and therapeutic complications in patients with Crohn's disease	Age at onset and phenotype		
Sharma 2019[168]	Natural history of children with mild Crohn's disease	Phenotype		
Smids 2017[169]	Candidate serum markers in early Crohn's disease: predictors of disease course		Multiple (36 markers)	
Sollelis 2019[170]	Combined evaluation of biomarkers as predictor of maintained remission in Crohn's disease	CDAI	CRP and calprotectin	
Song 2018[171]	Clinical characteristics and long-term prognosis of elderly-onset Crohn's disease	Age at onset and phenotype		
Stallmach 2019[172]	Predictive parameters for the clinical course of Crohn's disease: development of a simple and reliable risk model	Age at onset and phenotype	Haemoglobin and CRP	
Sun 2019[173]	Clinical features and prognosis of Crohn's disease with upper gastrointestinal tract phenotype in Chinese patients	Age at onset and phenotype		

TABLE 8 Summary of the potentially relevant research identified by an updated search performed in August 2020 (*continued*)

Study (first author and year)	Title	Clinical biomarker(s)	Serological biomarker(s)	Genetic biomarker(s)
Szántó 2018[174]	Biological therapy and surgery rates in inflammatory bowel diseases – data analysis of almost 1000 patients from a Hungarian tertiary IBD centre	Age at onset and phenotype		
Torres 2016[175]	Predicting outcomes to optimize disease management in inflammatory bowel diseases	Age at onset and phenotype	Multiple	Multiple loci
Wang 2018[176]	Study of disease phenotype and its association with prognosis of paediatric inflammatory bowel disease in China	Porto criteria and Paris classification		IL-10 receptor A
Wu 2019[177]	Serum protein biomarkers of fibrosis aid in risk stratification of future stricturing complications in pediatric Crohn's disease	Phenotype	ASCA-IgA and CBir	
Ye 2017[178]	Fecal calprotectin is a strong predictive marker of relapse in Chinese patients with Crohn's disease: a two-year prospective study		Calprotectin	
Zhao 2019[179]	A 10-year follow-up study of the natural history of perianal Crohn's disease in a Danish population-based inception cohort	Phenotype		
Zhulina 2016[180]	The prognostic significance of faecal calprotectin in patients with inactive inflammatory bowel disease		Calprotectin	
Ziv-Baran 2018[181]	Response to treatment is more important than disease severity at diagnosis for prediction of early relapse in new-onset paediatric Crohn's disease	PCDAI, age and phenotype	CRP and calprotectin	

EIM, extra-intestinal manifestation; FHx, family history; GWAS, genome-wide association study; HBI, Harvey–Bradshaw Index; MRI, magnetic resonance imaging; OmpC, outer membrane porin C; PCDAI, Paediatric Crohn's disease activity index; PLT, platelets.

Chapter 6 Discussion

The research detailed in this monograph is a response to the NIHR HTA programme call of 2014, HTA 14/210, 'Prognostic markers in early Crohn's disease'. The outcomes stipulated by the HTA programme in their commissioning brief were '[a]n overview of current evidence' and '[a] signal as to which biomarkers may be most useful'. Although a large amount of existing research has investigated the potential of a multitude of biomarkers to predict severe Crohn's disease, individual studies are usually small, single centre and restricted to one or a handful of biomarkers. Furthermore, results from individual studies often diverge, providing no clarity. The consequence is that individual clinicians cannot synthesise these data in a way that is meaningful for individual patients. In response to the brief, we have carried out a comprehensive overview across all biomarker types, the findings of which are detailed in this report. Although we identified seven previous systematic reviews that investigated associations between severe Crohn's disease and mostly serological and some genetic biomarkers, many confounded biomarker associations with both current disease (i.e. a diagnostic role) and future disease (i.e. a prognostic or predictive role), with no distinction between the two roles.

To generate meaningful results, we stipulated an a priori criterion that excluded biomarkers with insufficient evidence (defined by us as fewer than five component primary studies), and considered meta-analysis only where data for an individual biomarker could be extracted from three or more studies. Given the potential literature – we identified nearly 30,000 abstracts – we encountered relatively few genuinely prognostic studies, that is studies that investigated the development of future severe disease. We were surprised that common biomarkers, such as CRP, white blood cell count and haemoglobin, were rarely investigated despite being in widespread clinical use. We found no endoscopic, radiological or histopathological biomarkers that were sufficiently examined for meaningful meta-analysis. Although we anticipated an inevitable delay between validation of new biomarkers and subsequent prognostic studies, we were surprised that well-established biomarkers were poorly researched. This dearth of research may reflect researcher preoccupation with novel biomarkers, publication bias towards novel biomarkers or bias against studies finding no benefit.

Ultimately, across all biomarker types we identified only 71 individual studies with prognostic data, representing just 56 non-overlapping patient cohorts. From these, this report presents a meta-analysis of 11 potential predictors, of which eight displayed some evidence of predictive utility following meta-analysis. We present results for *NOD2* (any variant), the genetic predictor quoted in clinical guidelines as being associated with an increased risk of severe disease. We present a meta-analysis of three serological biomarkers, finding both ASCA-positive and anti-CBir1-positive patients to be at a higher risk of severe disease. It may be that biomarker levels vary too widely to be useful; acute phase reactant levels probably represent the patient status at diagnosis, for example during a flare. The levels of antimicrobial antigens at subsequent times remain uncertain. Although studies with paired sera at 5-year intervals imply stability, others suggest that levels of antimicrobial antigens change with disease progression and treatment. We excluded research without baseline serum draw. To have clinical utility, biomarkers must be prognostic in early disease.

We meta-analysed seven clinical predictors: Montreal behaviour, age, disease duration, disease location, smoking, sex and family history. Five of these showed prognostic potential (sex and family history did not). The strongest association with subsequent severe disease across the entire review was found for Montreal B2 and B3 categories, with ORs of 4.09 and 6.25, respectively. Meta-analysis also suggested that increased risk of developing severe disease was associated with perianal disease, longer disease duration and smoking. We found that the risk of subsequent severe disease was potentially decreased in patients who were diagnosed at a younger age and in those with any colonic disease or colonic disease alone.

Our review does have limitations, the majority of which are contingent on the quality of the primary component studies and difficulties with definitions of severe disease. As noted already, we found that true prognostic research was relatively scarce and was often reported confounded with diagnosis. Moreover, methods were heterogeneous and we were obliged to meta-analyse across different methods of biomarker measurement, different positivity thresholds and different follow-up durations. Such variability probably underlies the disparity between study effect estimates displayed, as seen, for example, in the ASCA forest plot.

Because data were heterogeneous, we stress that interpretation of our findings should focus on which biomarkers were found to have predictive potential rather than the precise strength of that prediction. Readers should not draw conclusions regarding the effectiveness of different predictors given that our estimates are based on results from different studies. Particularly for serological markers, the number and quality of studies are presently such that findings from future studies will be important; the majority of genetic and serological biomarkers that were identified were examined by insufficient studies for meaningful meta-analysis.

Furthermore, results from individual studies probably differ because of varying patient populations, study designs or outcome definitions. For example, we were obliged to use a range of definitions for 'severe' disease because there is no single universally accepted/reported definition. Where the measure is relatively inclusive, for example Beaugerie *et al.*,[18] around 60% of patients will have 'disabling disease' within 5 years. Conversely, although the Liege criteria define severity more precisely,[20] no article in our review stated the extent of intestinal surgery with detail sufficient to allow post hoc classification; single, early ileocaecal resection may be curative. Subsequently, only Loly *et al.*[20] (who proposed the Liege criteria) published data using this end point.

It is also possible that patients undergoing complex, expensive serological testing at diagnosis may be spectrum-biased towards severe disease. It is self-evident that biomarkers predictive of future severe disease have no clinical utility when such disease is established at diagnosis. For example, we were careful not to use Montreal B3 at baseline to predict development of B3 disease. B1, B2 and B3 are used mostly as predictors of surgery. We found that young age was not predictive of severe disease. However, children often display a panenteric phenotype that precludes surgical therapy, even when disease is severe.

We found considerable ROB, mostly because of suspected reporting bias as studies reported fewer than three standard predictors with non-significant results and results were not reported for standard follow-up times. Accordingly, no results were available for follow-up extending 5 to 10 years. Our analyses included some retrospective studies recruiting before 2004. Current treatment paradigms are evolving rapidly, and it is unclear whether or not biomarkers will behave similarly pre- and post-biologic introduction; we present individual study results with information sufficient for readers to explore this. Likewise, it was beyond our remit to consider anti-TNF response/failure to respond/loss of response. Recent studies have found that this in itself may identify patients destined to develop severe disease.[182,183] Predictive studies of multigene assays are currently under way, but we identified insufficient existing research for their inclusion in this review.

Owing to the large number of citations identified, we were unable to perform initial independent abstract screening by two reviewers; Darren Boone screened all abstracts alone. However, any uncertainty regarding eligibility, no matter how minor, was raised with Lucinda Archer (a statistician) initially and the with other members of the team if any uncertainty persisted. However, it is possible that some relevant data were discarded on the initial sift by using a single researcher. All full-text articles retrieved were screened independently by Sue Mallett (the senior statistician) to verify that data extraction for meta-analysis was correct, in particular to make the distinction between diagnostic and prognostic material.

This work has taken a considerable amount of time and resource, which was largely because of the nature of the prognostic reviews in diagnosis. Diagnostic studies remain poorly and imprecisely indexed in comparison with studies of therapeutic interventions. This problem is confounded further when the aim is to separate diagnostic from prognostic information, which is often confounded within

the same article (as explained elsewhere). The result is that search strings must be inclusive to avoid missing important data, but this inflates the amount of primary research that must be examined. We carried out an updated search in August 2020 to attempt to quantify the number of potentially relevant data subsequent to our original search. We identified an additional 4005 indexed articles in PubMed and 6878 in EMBASE, yielding 80 potentially relevant full-text papers. We estimate that around 23 of these would ultimately yield useful prognostic data, the large majority dealing with clinical biomarkers. Accordingly, we do not believe that our research has missed important serological or genetic biomarker research and we believe that our findings are likely to stand overall.

In summary, we carried out a systematic review of biomarkers potentially predictive of subsequent severe Crohn' disease, across all biomarker types, and focused on those contained in clinical guidelines. We found that prognostic research was heterogeneous and at a high ROB, and relatively few biomarkers relevant to clinical guidelines were investigated sufficiently for meta-analysis. Of those that were, we found evidence of prognostic potential for two serological (ASCA and anti-CBir1), one genetic (*NOD2*) and five clinical biomarkers (Montreal behaviour, age, disease duration, disease location and smoking). Considerably more prognostic research in this area is required, with methodological rigour, informed by consensus agreement around definitions of severe disease and following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines,[184] so that study results can be used by other researchers.

Chapter 7 Conclusions and recommendations for future research

We can make two broad conclusions and recommendations that arise from the research presented in this monograph. The first is that the quality and extent of prognostic research to predict future disease severity is somewhat lacking. We recommend that funders consider commissioning studies that are clearly prognostic and methodologically sound, and that adhere to established reporting guidelines for prognostic research. Because of the evidence gaps we identified, any such research should investigate all potentially important predictors, not just those that are perceived as 'cutting-edge' and/or 'novel'.

The second recommendation stems from the predictors identified by our review and meta-analysis; in the face of the limitations that we describe, we have identified a limited number of relatively easily accessible predictors that could be combined and tested in a multivariable prognostic model. This model would aim to accurately predict those patients with a new diagnosis of Crohn's disease who are destined to develop severe disease in the future, thereby facilitating individualised, early, targeted biological therapy. At the time of writing, we are currently developing and validating such a model using historic data obtained from the Royal Devon and Exeter NHS Trust; this work has been interrupted by the 2020 covid-19 pandemic that required clinical academics to return to full-time clinical work. It is our intention to complete this work when possible. If that validation proves sufficiently promising, we will ask that funders consider commissioning an external validation and/or clinical trial. Although the cleanest methodology would be to randomise application of the predictive model, this may prove ethically difficult given the widespread use of biological therapies currently. Due consideration should, therefore, be given to use of historic databases.

As noted elsewhere, because the existing literature is deficient it is likely that we have 'missed' some potentially important predictors simply because they have not been assessed sufficiently at the time of writing. As a result, development of a multivariable model should be flexible and not be restricted to the predictors identified by us. Development and validation could also incorporate multigene arrays, which are garnering considerable current interest: their incremental benefit (or otherwise) can then be quantified by their effect on prediction when added as one of the variables within an existing prognostic model based on more easily accessible data.

The work described in this monograph has not had substantial PPI input because it is a review of existing research performed by others. By contrast, we will seek PPI input from our expert patient collaborator when we have completed our planned work on the predictive model. Specifically, to inform clinical implementation of any model, we need to understand, from a patient perspective, how the presumed benefits of early biological therapy might be weighed against potential harmful side effects. These considerations must be made within the context of predictive accuracy, namely the degree to which the model may deny biological therapy to some deserving patients while simultaneously over-treating others.

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Contributions of authors

Steve Halligan (https://orcid.org/0000-0003-0632-5108) drafted the initial manuscript.

Darren Boone (https://orcid.org/0000-0002-3178-9791) performed the literature search, performed the majority of the data extraction and revised the initial manuscript.

Lucinda Archer (https://orcid.org/0000-0003-2504-2613) performed the majority of the data extraction and the statistical analysis, and revised the initial manuscript.

Tariq Ahmad (https://orcid.org/0000-0002-6058-5528) revised the initial manuscript.

Stuart Bloom (https://orcid.org/0000-0002-6361-4662) revised the initial manuscript.

Manuel Rodriguez-Justo (https://orcid.org/0000-0001-5007-1761) revised the initial manuscript.

Stuart A Taylor (https://orcid.org/0000-0002-6765-8806) revised the initial manuscript.

Sue Mallett (https://orcid.org/0000-0002-0596-8200) performed the majority of the data extraction and the statistical analysis, and drafted the initial manuscript.

All of the authors made substantial contributions to the interpretation and intellectual content, agree to be accountable for all aspects of the work, and gave final approval of the version of the report to be published. Professor Steve Halligan is guarantor.

Data-sharing statement

The research described in this monograph is a systematic review of available indexed literature; for this reason, all of the primary studies are available, in line with the stipulations of the individual journals concerned. The complete data extraction table used for this review can be obtained by contacting the corresponding author.

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