Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis
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CRD summary
This review concluded that faecal calprotectin testing was useful to identify patients most likely to need endoscopy for suspected inflammatory bowel disease and is more accurate in excluding the disease in studies of adults. Given potential for bias in the review and evidence of considerable heterogeneity, the authors’ recommendation to interpret the findings with caution appears appropriate.

Authors' objectives
The assess whether the number of unnecessary endoscopic procedures were reduced when faecal calprotectin testing was included in the investigation of patients with suspected inflammatory bowel disease.

Searching
MEDLINE and EMBASE were searched up to October 2009 for articles published in English. Search terms were reported. References of identified studies were searched manually.

Study selection
Prospective studies that compared diagnostic accuracy of faecal calprotectin testing (stool sampling index test) versus endoscopy and histopathology of segmental biopsy samples (reference standard) in patients with suspected inflammatory bowel disease based on clinical grounds were eligible for inclusion. Eligible studies were required to report whether addition of faecal calprotectin testing reduced the number of unnecessary endoscopies. Studies were required to proved sufficient data to permit construction of a 2x2 table.

Most studies were conducted in tertiary care facilities and were of outpatients. Patients were adults aged between 16 and 88 years or children and teenagers aged between 10 months and 19.9 years. The reference standard for adults was colonoscopy with or without histology and for children and teenagers was colonoscopy and histology, with or without upper gastrointestinal endoscopy. Some studies used ileal intubation. Most studies included patients with rectal bleeding. Most studies used the same faecal calprotectin assay. The cut-off value ranged from 24μg/g to 150μg/g.

Two reviewers independently screened studies for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed using seven criteria from the QUADAS checklist: representative spectrum of patients; diagnostic accuracy of reference standard; sample verification using a reference standard; use of the same reference standard regardless of index test used; appropriate time lapse between reference standard and index test to ensure the target condition was the same for both tests; reference standard results interpreted blind to index test findings; and explanation of withdrawals. Each criterion was scored as yes, no or unclear. No summary score was calculated. Further details on scoring were reported in the review

The authors did not state how many reviewers performed validity assessment.

Data extraction
Outcome data were extracted to calculate sensitivity and specificity. Where insufficient information was provided, primary authors were contacted.

The authors did not explicitly state how many reviewers performed data extraction.
Methods of synthesis
Sensitivity and specificity and their 95% confidence intervals (CIs) were combined by age group (adults or children and teenagers) using meta-analysis, weighted by sample size. Summary receiver operating characteristic curves were calculated.

A Fagan plot was used to calculate the effect of using faecal calprotectin testing on the post-test probability of inflammatory bowel disease expressed as positive and negative likelihood ratios.

The authors reported that they undertook subgroup analyses by age group using a cut-off value of 50μg/g or less and more than 50μg/g. They investigated the effect of prevalence of inflammatory bowel disease on specificity and the effects of exclusion of patients with rectal bleeding and quality criterion on the results.

Results of the review
Thirteen prospective studies were included in the review: six in adults (n reported as 670, but table of characteristics totalled 660); and seven in children and teenagers (n=371). Studies of children and teenagers were of greater quality than studies of adults. Three adult studies had selection bias and four adult studies did not use ileal intubation or histology was not undertaken. Verification bias was evident in two adult studies. Three studies of children and teenagers and two studies of adults did not provide reasons for withdrawal. Three studies were not blinded to index test results.

For adults (six studies), pooled sensitivity was 0.93 (95% CI 0.85 to 0.97) and pooled specificity was 0.96 (95% CI 0.79 to 0.99). For children and teenagers (seven studies), pooled sensitivity was 0.92 (95% CI 0.84 to 0.96) and pooled specificity was 0.76 (95% CI 0.62 to 0.86). There was a statistically significant difference between the lower specificity of children and teenagers and that of adults (p=0.048).

Inflammatory bowel disease was confirmed in 32% (n=215) adults and 61% (n=226) of children and teenagers (32% and 61% pre-test probability). Screening by faecal calprotectin levels had a significant effect on both age groups. An abnormal faecal calprotectin test result in adults increased the probability of inflammatory bowel disease to 91% (95% CI 77% to 97%) and a normal test result reduced the probability to 3% (95% CI 1% to 11%). In children, an abnormal test result increased the probability to 86% (95% CI 78% to 92%) and a normal test result reduced the probability to 15% (95% CI 7% to 28%).

Data on subgroup analyses and further investigations were not presented in the review, but the authors stated that subgroup analyses by cut-off value and further investigations showed no difference between the age groups.

The authors did not present formal assessment of statistical heterogeneity, but reported considerable heterogeneity among studies.

Authors’ conclusions
Faecal calprotectin levels were a useful screening tool to identify patients most likely to need endoscopy for suspected inflammatory bowel disease. The accuracy of faecal calprotectin screening to exclude the disease was significantly better in studies of adults than studies of children and teenagers. However, the findings should be interpreted with caution due to considerable heterogeneity.

CRD commentary
The review question was clearly defined and supported by appropriate inclusion criteria. The literature search was restricted to publications in English, so potentially relevant data may have been missed. The authors acknowledged potential for language bias. Study quality was assessed and was included as part of the analyses to some extent. The authors undertook study selection in duplicate, but it was unclear whether this was true for validity assessment and data extraction so reviewer error and bias could not be ruled out. The authors did not present any formal assessment of statistical heterogeneity, but they acknowledged evidence of heterogeneity. This may suggest that pooling of the results was not appropriate. The authors suggested that due to the potential for bias using the reference standard, the pooled sensitivity of faecal calprotectin may have been slightly overestimated. Given limitations with the included studies and the potential for bias in the review, the authors’ recommendations to interpret the findings with caution appear
Implications of the review for practice and research

Practice: The authors stated that patients with inflammatory bowel disease who were not diagnosed correctly should be balanced against patients without the disease who went on to have endoscopy. Complications of endoscopy and anaesthesia were important considerations. The authors also stated that it was unclear whether the findings were applicable to primary care settings and should not be used to screen asymptomatic patients.

Research: The authors did not state any implications for research.

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