Magnetic resonance enterography compared with ultrasonography in newly diagnosed and relapsing Crohn's disease patients: the METRIC diagnostic accuracy study

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Scientific summary

The METRIC diagnostic accuracy study

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Scientific summary

Background

Crohn's disease is a chronic inflammatory bowel disease predominantly affecting the young and requiring lifelong therapy. The small bowel and/or colon are most commonly affected and diagnosis is based on a combination of clinical features, together with endoscopic, histopathological, biochemical and imaging findings. Management is contingent on disease extent, activity and the presence of extraluminal complications. Radiological imaging is fundamental to the comprehensive phenotyping of Crohn's disease, particularly in the small bowel, which is beyond the reach of colonoscopy. Several small bowel imaging techniques are currently utilised in the NHS, but ultrasonography and magnetic resonance enterography are favoured as they do not expose patients to ionising radiation. Small bowel ultrasonography has been established for many years and utilises standard technology widely available in the NHS, but uptake has been hampered by perceptions of reduced accuracy and concerns about operator dependence. Magnetic resonance enterography is a more recent innovation, requiring oral contrast and access to high-technology imaging platforms, which are comparatively restricted in many health-care settings. Although meta-analyses suggest that magnetic resonance enterography and ultrasonography have similar accuracy for diagnosing and staging Crohn's disease, the primary literature is of questionable quality and prospective multicentre comparative data are lacking. High-quality evidence is needed to guide implementation.

Objectives

The primary objective of the Magnetic Resonance Enterography or ulTRasound In Crohn's disease (METRIC) trial was to compare the diagnostic accuracy of magnetic resonance enterography and ultrasonography for the extent of small bowel Crohn's disease against a construct reference standard, incorporating 6 months of participant follow-up. We recruited from two cohorts of participants: those newly diagnosed and those with established Crohn's disease clinically suspected of luminal relapse. The secondary objectives were to investigate the accuracy in grading inflammatory activity of magnetic resonance enterography and ultrasonography, diagnostic accuracy in the colon of magnetic resonance enterography and ultrasonography, interobserver variability in interpretation of magnetic resonance enterography and ultrasonography, diagnostic impact of an oral contrast load prior to small intestine contrast-enhanced ultrasonography, effect of oral contrast agent type on magnetic resonance enterography distension quality and participant symptoms, impact of magnetic resonance enterography sequences on diagnostic accuracy and radiologist confidence, impact of ultrasonography and magnetic resonance enterography on clinician decision-making, and participant experience of magnetic resonance enterography and ultrasonography, and to carry out a cost-effectiveness analysis.

Methods

Study design

We performed a multicentre prospective cohort study. Ethics committee approval was granted in 2014. Participants were recruited from eight representative UK NHS teaching and general hospitals. Participants were eligible for the new diagnosis subgroup if they had been diagnosed with Crohn's disease in the 3 months preceding recruitment, or if Crohn's disease was strongly suspected based on imaging or endoscopic features but pending final diagnosis. Participants for whom the final diagnosis was not Crohn's disease were subsequently excluded. Participants eligible for the suspected relapse subgroup had established Crohn's disease and high clinical suspicion of relapse based on objective markers of inflammatory activity and/or symptoms suggestive of luminal stenosis and/or abnormal endoscopy. Participants were ineligible if they

were aged < 16 years, were pregnant or had magnetic resonance imaging contraindications. Consecutive (i.e. unselected) eligible participants underwent magnetic resonance enterography and ultrasonography in accordance with the standard protocols of their recruitment sites, in addition to any other enteric imaging or endoscopic investigations performed as part of usual clinical care. Magnetic resonance enterography and ultrasonography image outputs were interpreted by two different practitioners blinded to the findings of the other, and to all other imaging, endoscopic and clinical data other than the cohort to which the participant was recruited. Practitioners recorded the presence and activity of Crohn's disease in the small bowel and colon, together with any extraenteric complications. In total, 28 suitably experienced practitioners (27 radiologists and one sonographer) interpreted the magnetic resonance enterography and ultrasonography. If there was discrepancy between magnetic resonance enterography and ultrasonography for the presence or location of small bowel Crohn's disease, an 'arbiter' small bowel investigation was performed if one had not already been performed as part of usual care. We used the construct reference standard paradigm (multidisciplinary panel diagnosis) incorporating the concept of clinical test validation. Participants' clinical course was followed for 6 months. For each participant, the panel considered the results of all small bowel investigations and all additional information including endoscopies, surgical findings, histopathology and biochemical and clinical course and recorded its opinion on whether or not small bowel Crohn's disease or colonic Crohn's disease was present, and, if so, whether or not disease was active. We estimated that a sample size of 210 participants with small bowel Crohn's disease would give 90% power to detect a significant (10%) sensitivity difference between magnetic resonance enterography (83%) and ultrasonography (73%) for disease extent. Direct comparison of sensitivity and specificity differences between magnetic resonance enterography and ultrasonography in the same participants were calculated from paired data using bivariate multilevel participant-specific (conditional) random-effects models.

Analysis by segment used a population-averaged random-effects model (using logit including robust standard errors). In subsets of participants, we also investigated interobserver variability in interpretation of magnetic resonance enterography and ultrasonography, the impact of an oral contrast load prior to small intestine contrast-enhanced ultrasonography (compared with conventional ultrasonography) on diagnostic accuracy, the effect of magnetic resonance enterography oral contrast agent type on small bowel distension quality and participant symptoms, the impact of magnetic resonance enterography sequences (T2-weighted and steady-state free precession gradient echo images alone; T2-weighted and steady-state free precession gradient echo images and diffusion-weighted images; and T2-weighted and steady-state free precession gradient echo images, diffusion-weighted images and contrast-enhanced images) on radiologist accuracy, and participant experience of small bowel imaging using questionnaires, modelled the diagnostic impact of magnetic resonance enterography and ultrasonography on clinician decision-making and carried out a cost-effectiveness analysis.

Results

Overall, 518 patients were assessed for eligibility, of whom 183 were excluded. In total, 335 participants entered the trial, of whom 51 were excluded (31 did not have Crohn's disease, two were lost to follow-up, 10 did not undergo magnetic resonance enterography and/or ultrasonography, six withdrew consent and two newly diagnosed participants underwent surgery without colonoscopy). The final cohort consisted of 284 participants (133 and 151 in new diagnosis and suspected relapse cohorts, respectively). There were no reported adverse events. Based on the reference standard, 233 (82%) participants had small bowel Crohn's disease, which was active in 209 (90%) participants, 129 (45%) participants had colonic Crohn's disease, which was active in 126 (98%) participants, 21 participants had enteric fistulae and seven had intra-abdominal abscess. For small bowel Crohn's disease extent, magnetic resonance enterography sensitivity [80%, 95% confidence interval (CI) 72% to 86%] was significantly greater than ultrasonography sensitivity (70%, 95% CI 62% to 78%), with a difference of 10% (95% CI 1% to 18%; $p = 0.027$). For small bowel Crohn's disease extent, magnetic resonance enterography specificity (95%, 95% CI 85% to 98%) was also significantly greater than ultrasonography specificity (81%, 95% CI 64% to 91%), with a difference of 14% (95% CI 1% to 27%). For small bowel Crohn's disease presence, magnetic resonance

enterography sensitivity (97%, 95% CI 91% to 99%) was significantly greater than ultrasonography sensitivity (92%, 95% CI 84% to 96%), with a difference of 5% (95% CI 1% to 9%). For small bowel Crohn's disease presence, magnetic resonance enterography and ultrasonography specificity was 96% (95% CI 86% to 99%) and 84% (95% CI 65% to 94%), respectively. There were no overall significant differences in sensitivity or specificity between magnetic resonance enterography and ultrasonography for colonic Crohn's disease extent or presence. Sensitivities of magnetic resonance enterography and ultrasonography for small bowel Crohn's disease presence and extent in the new diagnosis and suspected relapse cohorts were very similar to those sensitivities estimated across all participants, although for colonic Crohn's disease presence ultrasonography sensitivity (67%, 95% CI 49% to 81%) was significantly greater than magnetic resonance enterography sensitivity (47%, 95% CI 31% to 64%) in the new diagnosis cohort, with a difference of 20% (95% CI 1% to 39%). For active small bowel Crohn's disease, magnetic resonance enterography sensitivity (96%, 95% CI 92% to 99%) was significantly greater than ultrasonography sensitivity (90%, 95% CI 82% to 95%), with a difference of 6% (95% CI 2% to 11%). Magnetic resonance enterography detected five out of seven (71%) abscesses and 18 out of 21 (86%) enteric fistulae, whereas ultrasonography detected three out of seven (43%) abscesses and 11 out of 21 (52%) enteric fistulae.
A total of 186 participants had a colonoscopic standard of reference against which magnetic resonance enterography had a sensitivity of 97% (95% CI 91% to 99%) and ultrasonography has a sensitivity of 91% (95% CI 79% to 97%) for terminal ileal disease presence, which was not statistically significant.

Small intestine contrast-enhanced ultrasonography

In total, 64 participants underwent small intestine contrast-enhanced ultrasonography. Compared with ultrasonography, sensitivity and specificity were identical for small bowel Crohn's disease extent (71%, 95% CI 58% to 81%, and 86%, 95% CI 49% to 97%, respectively).

Interobserver agreement

Ultrasonography

In total, 38 participants (11 and 27 in the new diagnosis and suspected relapse cohorts, respectively) underwent ultrasonography twice, performed by two practitioners from a pool of seven. For the presence of small bowel Crohn's disease, both reads agreed with the consensus reference standard for 9 out of 11 (82%) participants in the new diagnosis cohort (prevalence-adjusted bias-adjusted $\kappa = 0.64$) and 22 out of 27 (81%) participants in the suspected relapse cohort (prevalence-adjusted bias-adjusted $\kappa = 0.63$), suggesting substantial agreement for both cohorts. Agreement for small bowel Crohn's disease extent was at best only fair [64% agreement with the consensus reference standard in the new diagnosis cohort (prevalence-adjusted bias-adjusted $\kappa = 0.27$) and 56% agreement with the consensus reference standard in the suspected relapse cohort (prevalence-adjusted bias-adjusted $\kappa = 0.11$)]. Agreement for the presence of colonic Crohn's disease was inferior to that for small bowel Crohn's disease.

Magnetic resonance enterography

A total of 73 magnetic resonance enterography data sets (28 in the new diagnosis cohort and 45 in the suspected relapse cohort) were each read by three radiologists from a pool of 27. For the presence of small bowel Crohn's disease, in the new diagnosis cohort, on average, reads agreed with the consensus reference standard for 18 out of 26 (69%) disease-positive participants and one out of two (50%) disease-negative participants (prevalence-adjusted bias-adjusted $\kappa = 0.36$), indicating fair agreement. In the suspected relapse cohort, on average, reads agreed with the consensus reference standard for 25 out of 33 (76%) disease-positive participants and 9 out of 12 (75%) disease-negative participants (prevalence-adjusted bias-adjusted $\kappa = 0.51$), indicating moderate agreement. Agreement for small bowel Crohn's disease extent was at best only slight [53% agreement with the consensus reference standard (prevalence-adjusted bias-adjusted $\kappa = 0.07$) in the suspected relapse cohort and 43% agreement with the consensus reference standard (prevalence-adjusted bias-adjusted $\kappa = -0.14$) in the new diagnosis cohort]. Agreement for the presence of colonic Crohn's disease was inferior to that for small bowel Crohn's disease.

Participant experience

A total of 159 participants completed all or part of the experience questionnaire. Overall, 88% (128/145) of participants rated magnetic resonance enterography as very or fairly acceptable, which is significantly lower than the percentage (99%; 144/146) of participants who rated ultrasonography as very or fairly acceptable. Participants were slightly less willing to undergo magnetic resonance enterography again (91%; 127/140) than to undergo ultrasonography again (99%; 133/135). On a scale of 1 (least) to 7 (most), test burden scores were generally low, although magnetic resonance enterography generated greater burden than ultrasonography (mean 2.72 vs. mean 1.66, respectively; $z = 9.5$). Younger age and emotional distress were associated with greater magnetic resonance enterography and ultrasonography burden. In a direct test comparison, the majority (80%; 100/125) preferred ultrasonography to magnetic resonance enterography, but participants prioritised diagnostic accuracy over scan burden.

Effect of oral contrast type

Full data were available for 66 participants (47 ingesting mannitol-based contrast agents and 19 ingesting polyethylene glycol-based contrast agents). There was no difference in segmental distension quality between the two contrast types. Distension of the jejunum, ileum and terminal ileum were rated as excellent or good in 27% (13/47), 65% (31/47) and 43% (20/47), respectively, of the mannitol group compared with 16% (3/19), 63% (12/19) and 42% (8/19), respectively, of the polyethylene glycol group. The participants' symptom profiles were also very similar between the two agents.

Sequence selection

A total of 73 magnetic resonance enterography data sets (28 in the new diagnosis cohort and 45 in the suspected relapse cohort) were each read by three radiologists from a pool of 27. There was no increase in sensitivity or specificity for small bowel Crohn's disease extent with the addition of diffusion-weighted images to T2-weighted and steady-state free precession gradient echo images. However, compared with T2-weighted and steady-state free precession gradient echo images alone (sensitivity for small bowel Crohn's disease extent 63%, 95% CI 51% to 75%), the addition of contrast-enhanced images led to a significant drop in sensitivity to 56% (95% CI 42% to 68%), a difference of 7% (95% CI –1% to –14%).

Modelling of the diagnostic impact of magnetic resonance enterography and ultrasonography

Out of 158 included participants, 74 were new diagnosis participants and 84 were suspected relapse participants. Therapeutic decisions based on clinical information and magnetic resonance enterography alone agreed with the final reference standard treatment decision category (based on all available information) for 122 out of 158 (77%) participants and disagreed for 36 out of 158 (23%) participants. Therapeutic decisions based on clinical information and ultrasonography alone agreed with the reference standard treatment decision category for 124 out of 158 (78%) participants and disagreed for 34 out of 158 (22%) participants.

Cost-effectiveness

There were no differences in costs or quality-adjusted life-years between magnetic resonance enterography and ultrasonography. For the new diagnosis cohort, the net monetary benefits for magnetic resonance enterography and ultrasonography were not significantly different, at £7288 (95% credibility interval £4797 to £9111) and £7513 (95% credibility interval £4936 to £9392), respectively, giving an incremental net monetary benefit for magnetic resonance enterography versus ultrasonography that was not significantly

different from zero (–£225, 95% credibility interval –£1085 to £713). For the suspected relapse cohort also, the net monetary benefits for magnetic resonance enterography and ultrasonography were not significantly different [£4020 (95% credibility interval £2426 to £5488) and £4321 (95% credibility interval £2696 to £5787), respectively], giving a non-significant incremental net monetary benefit for magnetic resonance enterography versus ultrasonography of –£301 (95% credibility interval –£993 to £305). Sensitivity analyses showed little uncertainty in these findings.

Conclusions

We found that both ultrasonography and magnetic resonance enterography achieve excellent diagnostic accuracy for the extent and activity of small bowel Crohn's disease in both new diagnosis and suspected relapse participants, but that magnetic resonance enterography has superior sensitivity for small bowel Crohn's disease presence, extent and activity.

Implications for health care

In a NHS setting, magnetic resonance enterography has significantly higher sensitivity and specificity than ultrasonography for the presence and extent of small bowel Crohn's disease, although both tests are valid first-line investigations. Ultrasonography performs better than magnetic resonance enterography for detection of colonic Crohn's disease in those patients newly diagnosed but is inferior to colonoscopy. Both magnetic resonance enterography and ultrasonography are deemed acceptable by the majority of patients, although ultrasonography induces less patient burden and is generally preferred. However, patients rank diagnostic accuracy as more important than test burden. Interobserver agreement is variable between practitioners, particularly for disease extent, which should be considered. We found no evidence than one oral contrast agent is better than another in achieving good bowel distension during magnetic resonance enterography or reducing patient symptom load. We also found no evidence that small intestine contrast-enhanced ultrasonography increases diagnostic accuracy for small bowel Crohn's disease extent compared with conventional ultrasonography. Addition of diffusion-weighted imaging does not improve the accuracy of magnetic resonance enterography protocols based only on T2-weighted steady-state free precession gradient echo images, and post-contrast images may be detrimental to sensitivity. Modelled diagnostic impact on clinician therapeutic strategy was similar between magnetic resonance enterography and ultrasonography. There is no reason to prefer magnetic resonance enterography or ultrasonography on economic grounds.

Recommendations for future research

Future research should investigate:

- the role of ultrasonography in targeted follow-up of Crohn's disease patients with an established disease phenotype, and the utility of magnetic resonance enterography and ultrasonography in treatment response assessment
- the most clinically effective and cost-effective cross-sectional imaging investigation in patients with non-specific abdominal symptoms to confirm or refute a diagnosis of Crohn's disease
- the impact of dedicated training programmes and clinical case volumes on practitioner accuracy.

Trial registration

This trial is registered as ISRCTN03982913.

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