# TITLE PAGE

## Article Title:

**Aberrant motility in unaffected small bowel is linked to inflammatory burden and patient symptoms in Crohn's Disease**

## Short Title:

**Aberrant small bowel motility in Crohn's disease**

## Authors

**Menys A[1]., Makanyanga J[1]., Plumb A[1]., Bhatnagar G[1]., Atkinson D[1]., Emmanuel A., & Taylor SA[1].**

*1. Centre for Medical Imaging, UCL, 3rd Floor East, 250 Euston Road, London, NW1 2PG*

*2. University College London Hospitals, Gastroenterology London, United Kingdom NW1 2PG*

## Corresponding Author:

**Prof Stuart A. Taylor**

stuart.taylor@ucl.ac.uk

Centre for Medical Imaging

3rd Floor East

Euston Road

NW1 2PG

## Abstract

Objectives: Inflammation related enteric dysmotility has been postulated as a cause for abdominal symptoms in Crohn's disease (CD). We investigated the relationship between MRI-quantified small bowel (SB) motility, inflammatory activity and patient symptom burden.

Methods: The Harvey Bradshaw Index (HBI) and fecal calprotectin were prospectively measured in 53 CD patients (median age 35, range 18-78) the day before MRI enterography which included a dynamic (cine), breath-hold motility sequence, repeated to encompass the whole SB volume. A validated registration based motility quantitation technique produced motility maps and regions of interest were drawn to include all morphologically normal SB (i.e. excluding diseased bowel). Global SB motility was correlated with calprotectin, HBI and symptom components (wellbeing, pain, diarrhea). Adjustment for age, sex, smoking and surgical history was made using multivariate linear regression.

Results: Median calprotectin was 336 (range 0-1280). Mean HBI, motility mean and motility variance were 3 (range 0-16), 0.33 (0.18 to 0.51) and 0.01 (0.0014 to 0.034) respectively. Motility variance was significantly negatively correlated with calprotectin (Rho = -0.33, P = 0.015), total HBI (rho = -0.45, P <0.001), wellbeing (rho= -0.4, p=0.003), pain (rho = -0.27, p =0.05) and diarrhea (rho= -0.4, p=0.0025). The associations remained highly significant after adjusting for

covariates. There was no association between mean motility and calprotectin or HBI ($p>0.05$).

Conclusions: Reduced motility variance in morphologically normal small bowel is associated with patient symptoms and fecal calprotectin levels, supporting the hypothesis that inflammation related enteric dysmotility may explain refractory abdominal symptoms in CD.

## WHAT IS CURRENT KNOWLEDGE

- Abdominal symptoms often persist in Crohn's disease patients despite successful immunosuppressive therapy and full mucosal healing.
- Irritable bowel syndrome symptoms are more common in Crohn's patients with raised calprotectin levels when in clinical remission.
- Aberrant small bowel motility remote from diseased segments has been postulated as a cause for refractory symptoms, although supportive data are limited.

## WHAT IS NEW HERE

- Reduction in the normal variability of small bowel motility quantified using cine MRI is associated with increased abdominal symptoms in CD patients and with disease related inflammatory burden based on faecal calprotectin
- Inflammation related enteric dysmotility may explain some abdominal symptoms in Crohn's disease (CD).

# Introduction

Crohn's disease (CD) manifests as lifelong, relapsing and remitting inflammation of the gut and is conventionally treated using immunosuppressives to reduce inflammation and subsequent bowel damage including stricturing and fistulation[1]. It is well recognized that there is a discord between apparent therapeutic success (such as endoscopic mucosal healing) and resolution of patient symptoms including pain, and general wellbeing [2,3]. Indeed, 20% of patients achieving near endoscopic normality after treatment have little or no improvement in symptom burden[4,5].

Gut inflammation, whether mediated by abnormal immune response or via infection, has been consistently demonstrated to alter gut function in pre-clinical models and likely occurs via a combination of structural, neuronal, immunological and hormonal changes [6–10]. These changes lead to abnormal secretion, sensation and motility of the gut which could precipitate functional symptoms including abdominal pain and diarrhea [11–13]. Oro-cecal transit time for example has been shown to be reduced in active CD[14] whilst gastric emptying is apparently attenuated [15,16]. Furthermore, irritable bowel syndrome type symptoms are more common in Crohn's patients with raised calprotectin even when clinically otherwise in remission[17].

To date, limited data regarding aberrant motility in IBD has been derived by assessing transit (using radiographic markers or radiolabelled foodstuffs) or via invasive manometric measurement[18,19]. Whilst validated for functional conditions, their utility in IBD has not been established. More recently, MRI with quantitative analysis has been used to non-invasively explore segmental and whole gut motility[20–24]. In a small pilot study of 13 CD patients, Bickelhaupt et al found a negative relationship between intestinal motility and inflammatory markers (CRP and faecal calprotectin (fC)) in apparently normal bowel[21]. Such data suggests that simple cine MRI motility sequences, easily added to standard MR enterography protocols, could provide greater insight into deregulated motility in CD and its role in the etiology of patient symptoms.

The aim of this prospective study was to investigate the relationship between MRI quantified intestinal motility in morphologically normal bowel against i) inflammatory and ii) subjective symptom burden measured by faecal calprotectin and Harvey Bradshaw index respectively in patients with CD.

# Methods

## Patient selection

Consecutive patients with known or suspected Crohn's disease and referred for MR enterography were recruited prospectively at a single center between February 2010 and October 2011.

In patients with suspected CD, only those patients with a final positive diagnosis based on clinical, biochemical, endoscopic, imaging and histopathological findings were ultimately included in the current study. Research ethics committee approval (Hampstead REC, North London) was obtained and all patients gave informed written consent.

Patients completed a Harvey Bradshaw Index (HBI) symptom questionnaire the day before the MRI[25] and provided a stool sample on the morning of the MRI to facilitate same-day measurement of fecal calprotectin (fC) (PhilCal; NovaTec Immunodiagnostica, Dietzenbach, Germany). Individual responses to HBI parameters of diarrhea, pain and wellbeing were recorded. Demographic data including age, sex, disease duration, Crohn's disease related medication, smoking status, body mass index and surgical history were also documented. The patient cohort has in part been previously been described by Makanyanga et al[26] but here we report analysis of motility data, which has not previously been described. For the purposes of the current study, patients were excluded if they had a stoma, failed to undergo dynamic MRI cine sequences (see below) or were taking

medication with known motility altering affects including pro-kinetic and antiemetic agents, spasmolytic (including Buscopan) and opioid analgesics.

## MRI Protocol

Magnetic Resonance Enterography (MRE) was performed using standardized clinical protocols on either a 1.5T (Avanto, Siemens, Medical Systems, Erlangen, Germany) or 3T (Achieva; Philips, Best, The Netherlands) unit. Patients fasted for 4 hours before ingesting 1 to 1.5L of 0.2% locust bean gum/2.5% mannitol solution over 45 min. The MRE protocol commenced with dynamic, motility 'cine' imaging (Appendix 1) before hyoscine butylbromide was administered and anatomical sequences were performed.

Trained MRI radiographers acquired single-plane time series images with a 1cm slice thickness to capture bowel motility. The temporal resolution at both field strengths was 1 image per second acquired over a 20s breath-hold. Each single slice breath hold motility acquisition was repeated multiple times moving the slice position sequentially from the posterior to the anterior abdomen, to encompass as much of the total small bowel volume as possible. Between 7 and 15 positions were required depending on body habitus.

## Motility assessment

Imaging datasets were anonymized and downloaded into a graphical user interface for motility analysis written in MATLAB (The MathWorks, Natick, MA, USA). All motility analysis was performed using validated software based on optic flow registration, including contrast changes[27]. A full description of the software has been previously published[27]. In brief, the registration algorithm corrects local deformation generated by bowel wall motion. The resulting set of deformation fields are analyzed by taking the standard deviation of each pixels Jacobian determinant through time to produce a parametric motility map, serving as a surrogate of bowel wall motion (figure 1A-D). Regions of interest (ROIs) can be manually applied to a particular segment or, alternatively, the entire bowel volume. This technique has been validated and shown to be repeatable and sensitive to drug-induced changes in motility [24]. It has previously been successfully applied in segmental CD [22] and Chronic Intestinal Pseudo-Obstruction[28].

Three motility metrics were implemented based on ROIs drawn by a gastroenterologist (4 years experience with MRE) in consensus with a GI radiologist with 9 years of experience in small bowel MRI, both blinded to all clinical information. For all metrics, only small bowel with a normal appearance across all acquired MRI sequences was sampled i.e. any small bowel with typical MRI stigmata of Crohn's disease such as mural thickening (>3mm), abnormal mural T2 signal and increased contrast enhancement was excluded in any ROI placement [29].

**Metric 1: Contractions per minute**

The contractions per minute is a semi-objective motility metric based on the change in luminal diameter of the bowel when observed in the coronal plane [21]. In detail, two linear regions of interest (ROIs) were placed, each in a different quadrant containing well-distended morphologically normal bowel remaining in plane throughout the cine time series. Regions were drawn on one frame of the selected time series across the lumen of the chosen loop (from outer bowel wall to outer bowel wall Figure 2A) and then automatically propagated through the series by the analysis software[27].

The number of contractions (defined as a reduction in luminal diameter of more than 10% of the overall mean for the 20 second breath hold time period) was recorded at each ROI and multiplied by 3 to give a number of contractions per minute (CPM) (figure 2B,C)[30,31]. The mean of the two CPM scores (i.e. one from each ROI) was taken as the measure of contractile activity.

Metric 2: mean global motility

The observers drew a ROI on one frame of each acquired cine time series to encompass the whole small bowel volume for each patient. Again, only morphologically normal bowel was included in the ROI and abnormal bowel, colon, static structures such as solid organs and mesenteric fat were excluded. If necessary, several large ROIs were drawn on the coronal image to encompass all visible normal small bowel (Figure 1). Previous reference ranges from a cohort of healthy volunteers suggested the mean small bowel contraction rate was 5cpm (range 0 to 15).

A mean global small bowel motility score was calculated by averaging the SD Jacobian parametric map values under each ROI across all the breath hold time series. Examples of low and high small bowel motility can be seen in figure 1A and 2B respectively. Previous reference ranges from a cohort of healthy volunteers suggested mean global motility (mean) score of 0.34 (Range 0.28 to 0.395)

Metric 3: Variance of global Motility

The same ROIs were utilized as per metric 2. However the variance of the SD Jacobian parametric map values under each ROI across the small bowel volume was calculated. A high motility variance score implies a large range of motility values across the small bowel volume i.e. bowel motion is heterogeneous. An illustrative example of the spread of mean motility and variance from the patient cohort is show in figure 1. Previous reference ranges from a cohort of healthy volunteers suggested mean global motility variance score of 0.03 (range 0.02 to 0.04)

## Statistical analysis

All data were assessed for normality using the Shapiro-Wilk test (alpha = 0.05); non-parametric statistics were used where data were non-normally distributed.

Correlation assessment between the 3 motility metrics, fC and HBI was performed using Spearman's Rho and then multivariate linear regression after accounting for the following covariates: Age, sex, current smoking status (smoker/non-smoker),

Crohn's disease specific medication (Table 1), previous history of surgery (yes/no), body mass index, and number of years since diagnosis. Correlation was also calculated between each of the HBI symptom parameters (wellbeing, pain and liquid stools) and each motility metric, subsequently repeated using ordinal logistic regression (for pain and wellbeing) and negative binomial regression (for number of diarrheal stools/day) to account for the same covariates as above. In addition, the fecal calprotectin level was included as a measure of total inflammatory burden. To determine the strength of association of each motility metric, a simpler regression model without that metric as a predictor was compared to the full model using the likelihood ratio test, with $p<0.05$ taken as being significant for all analyses. In addition a simple correlation was performed between a global MR disease activity score (Magnetic Resonance Enterography Global Score (MEGS) described in Makanyange et al. [26]) and the three motility metrics.

All statistical analysis was performed using MATLAB (The Mathworks, Natick, MA) or R for Mac version 3.0.1 (R Core Team, Vienna, Austria).

# Results

## Cohort Demographics

71 patients were recruited and underwent MRI enterography. Eighteen patients were excluded (10 female). 8 were taking motility influencing medication known to affect bowel motility, 6 had a stoma and 4 had missing dynamic sequences leaving a total of 53 subjects in the final study cohort (median age 35, range 18 to 78). Median disease duration was 6 years (range 0 to 32). 25 of the cohort had ileocolonic disease, 17 and 11 had isolated colonic and small bowel disease respectively. 14 of the 53 patients had a stricturing disease phenotype. A summary of patient demographics is presented in table 1.

## Motility metrics, fC and HBI

A summary of motility metrics, calprotectin level and HBI score is provided in table 2.

There was no significant correlation between fC and HBI, $R = -0.06$, $P = 0.65$ .

There was there no significant correlation between the MEGS score and motility assessed by global variance, global mean and CPM metrics ($R = -0.02$, $p = 0.88$, $R = -0.034$, $p = 0.8$ & $R = -0.09$, $p = 0.52$ respectively).

There was a statistically significant negative correlation between global small bowel motility variance (metric 3) and both fC and total HBI (r=-0.33, p=0.015 and R=-0.45, p<0.001 (figure 3) respectively). After applying the multivariate regression model, global small bowel motility variance retained a significant negative association with both fC (p=0.04) and HBI (p=0.0005). The regression models showed that for each 0.01 unit increase in global small bowel motility variance, there was an associated 2.5 unit drop in HBI and a 145 micrograms/g drop in fC.

Neither contraction rate per minute (metric1) nor mean global motility (metric 2) showed any significant relationship to fC or HBI (table 3), either by simple correlation or by multivariate regression.

## Stratified assessment of the Harvey-Bradshaw index indices

There was significant inverse correlation between global motility variance and wellbeing, abdominal pain and the number of liquid stools (table 4). These differences retained significance in the regression models following adjustment for covariates: Lower global motility variance scores were statistically significantly associated with worse HBI wellbeing scores (p=0.00046). Overall, for each 0.01 reduction in the global motility variance score, the odds of a patient giving a higher (ie worse) HBI wellbeing score increased by 0.19 (95% CI 0.06-0.50). Similarly, lower global motility variance scores were associated with higher pain scores (p=0.0043). For each 0.01 reduction in global motility variance, the

odds of a higher abdominal pain score increased by 0.26 (95% CI 0.08-0.67). Finally, the number of diarrheal stools/day was also significantly associated with lower global motility variance (p=0.0001), with each 0.01 reduction in global motility variance increasing the rate of an additional diarrheal stool by 0.39/day (95%CI 0.23-0.61). Of the other covariates assessed, smoking and BMI were significantly association with abdominal pain, and female sex and disease duration were significantly associated with the number of diarrheal stools (Table 5).

Contractions per minute and mean global motility were not significantly associated with wellbeing (p=0.30 and p=0.32 for CPM and mean global motility respectively), abdominal pain (p=0.66 and p=0.32) or number of diarrheal stools (p=0.34 and p=0.62).

## Discussion

This study has demonstrated a significant negative association between a global MRI measure of motility variance in apparently normal bowel and both inflammatory and symptom burden in CD.

Fecal calprotectin (fC) is a marker of mucosal CD activity, correlates with excretion of $^{111}$indium-labelled granulocytes in stool, CRP, faecal lactoferrin[32–36] and predicts active disease at endoscopy [37–39]. Despite several limitations it seems a reasonable marker of global inflammatory burden as an endpoint[40]. In

comparison, HBI is a widely used clinical disease severity score and includes patient self-reported components such as diarrheal stools, wellbeing and abdominal pain offering an important insight into the functional aspects of patient symptoms. As previously described, we found a poor correlation between these objective (calprotectin) and more subjective (HBI) markers of disease activity, underlining the apparent disconnect between inflammatory burden and patient symptoms[26,41].

Global bowel motility variance essentially measures the range of motility across the bowel taking into account the "peaks and troughs" between and within different segments. It is well established that there is a wide range of contractile activity in healthy individuals[42–47]. Contractility is split broadly into the post-prandial actions (peristalsis and segmentation) directed at mixing food and aiding absorption and the fasted contractility associated with maintaining bowel health and function[42]. In the post prandial state, contractility is varied, with periods of quiescence prolonging transit time to aid absorption[42,48,49]. Across the total small bowel volume it therefore follows that motility is heterogeneous (i.e. variable) in the postprandial state. It seems intuitive that the altered osmolality induced by mannitol, together with the increase in luminal volume, precipitates a largely post-prandial response in the gut. In support, healthy subjects demonstrate large variations in segmental motility on MRI following an oral contrast load [31].

We observed decreased motility variation in patients reporting more severe abdominal symptoms, supporting the concept that reduction in the expected heterogeneity of motility in the post prandial state may be directly related to

patient symptoms. Furthermore, each of the HBI symptom components (pain, wellbeing and diarrheal stools) were all individually correlated with a reduction in bowel motility variance. The association with diarrheal stools is interesting and possibly reflects a more sustained contractile action with a decrease in periods of quiescence required for efficient liquid absorption. The data appears robust as the association between motility and HBI components remained after accounting for other factors which may influence patient symptoms such as age, sex, surgical history, years since diagnosis and smoking. [46,50].

We also found a negative association between bowel motility variance and inflammatory burden quantified using fecal calprotectin. Our data therefore support the hypothesis that bowel inflammation inhibits the normal healthy variability in small bowel motility and that this, in turn, may contribute to functional symptoms such as pain and wellbeing. Indeed, Keohnae et al reported higher levels of calprotectin in patients with irritable bowel syndrome like symptoms, compared to those without in a cohort of CD patients clinically in remission suggesting low grade inflammation underpins abdominal symptoms[17]. Our data suggest aberrant motility may be a novel and measurable manifestation of this process.

Existing data on bowel motility in CD are sparse. MRI motility techniques have clearly shown reduced motility in affected segments which is directly related to the burden of mural inflammation [20,22]. However, data on motility in the unaffected bowel are limited. Investigations using conventional techniques such as transit times and manometry are heterogeneous with decreased transit time[14],

prolonged gastric emptying[15,16] and altered anorectal physiology all described [51,52]. A recent small study using MRI in 13 CD patients showed a strong, negative correlation between contraction frequency per minute in normal bowel segments and fC (R = 0.805, p = 0.001) [21]. In addition, a number of pre-clinical investigations relate even low-grade inflammatory activity to gut neuroplasticity (structural, synaptic or intrinsic changes that alter neuronal function) [53,54].

Although global small bowel motility variance was associated with both fC and HBI, our other measured motility metrics showed no relationship to these indices. In our larger cohort of patients we were unable to reproduce the data from Bickelhaupt et al[21]. It should be noted however that Bickelhaupt et al. acquired data over 60-90 seconds rather than our 20s breath-hold protocol. Although motility measured using CPM is perhaps the most widely reported metric it is subject to several limitations. Notably, placement of ROIs in morphologically normal bowel is subjective, and recent work has shown large intra-segmental contraction rate variability in healthy volunteers suggesting high dependence on ROI positioning[31]. Quantification of global (as opposed to segmental) motility using software analysis in the current study has been shown to be repeatable over time in healthy volunteers. In the current study, no relationship between mean global motility was found with either calprotectin or HBI[24]. This suggests average bowel motility itself may not be a strong marker of intestinal dysfunction, perhaps in part due to “averaging out” of more subtle changes, better detected by changes in motility variability.

There are several limitations in this study. Although two of our motility metrics (CPM and mean motility) are well described, the additional measure of motility variance is new. However use of this metric was based on the well described heterogeneity of small bowel motility in the existing literature. The three motility metrics against two outcomes may provide a source Type I statistical error, although we think this is unlikely. A second limitation is the use of a breath-hold protocol driving the observation of bowel motility where longer time periods might provide more robust data. However, the breath-hold technique is well validated and more practical for patients without the added analytical complexity introduced by free breathing. We standardized the preparation of our patient cohort prior to MRI, ensuring all patients were fasted and were provided with the same volume of oral contrast agent to be ingested over a standard time period. We also excluded patients on medication overtly affected bowel motility. However we were unable to control for other factors that could influence motility such as gender, time of day, caffeine use and smoking. Such influences would however likely not produce any systematic bias as would be applicable to the whole cohort. Furthermore we are able to account for the influence of several such as smoking, age and gender in our analysis. We blinded observers to all clinical information, although to ensure exclusion of all abnormal bowel they were unblinded to anatomical MRI sequences when placing ROIs. It would have been interesting to correlate motility in the healthy bowel against endoscopic disease severity in affected segments. However, endoscopic data was not universally available in this patient cohort.

Although we have shown a relationship between reduced motility variation and both patient symptoms and fecal calprotectin, we are unable to assume causality. Whilst we can hypothesize that aberrant motility is related to remote inflammation and may help explain functional abdominal symptoms, it maybe patients feelings of pain and wellbeing affects motility secondarily.

In conclusion, we have shown the motility variance in unaffected bowel quantified using MRI has moderate negative correlation with both patient symptoms and fecal calprotectin in CD patients.

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# Figure legends

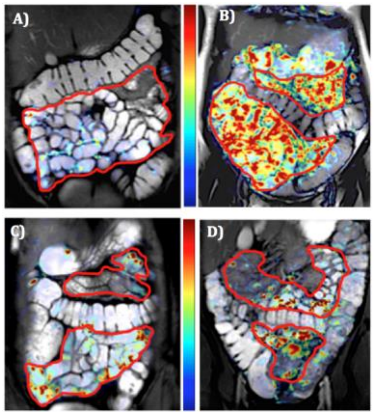


**Figure 1** Motility maps (red = high motility, blue = low motility) for 4 subjects with radiologist drawn ROIs (red) around morphologically normal small bowel. A: Low mean motility (0.04) low variance score (0.003). B: High mean motility (0.47), low variance score (0.005), C: Low mean motility (0.11) moderate variance score (0.025) & D: moderate mean motility (0.29), high variance (0.03).

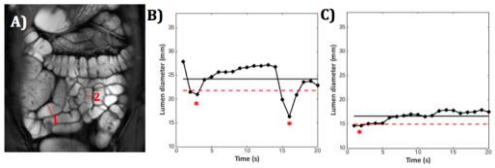


**Figure 2.** The contractions per minute (CPM) score was measured by plotting the change in luminal diameter over time and counting the number of instances where a decrease in bowel diameter was greater than 10% less than the mean bowel diameter for that time series. The two ROIs are depicted in 2A with the respective time curves for the two ROIs in 2B and 2C. Horizontal black line represents mean diameter, dotted red line the mean diameter minus 10% and the red stars signify significant contractions.

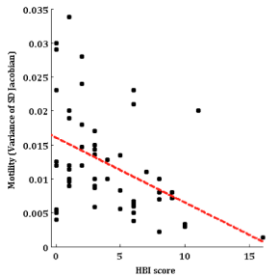


**Figure 3.** Scatter plot demonstrating a significant negative relationship between HBI score and global motility variance (Rho = -0.45, P <0.001).

## Table legends

| Parameter | Number of Patients |
|---|---|
| ***Disease Duration*** | |
| <1year | 5 |
| 1-5 year | 20 |
| 5-10 year | 14 |
| >10 year | 14 |
| ***Disease location*** | |
| Terminal ileal | 11 |
| Colon | 17 |
| Ileocolonic | 25 |
| ***Medications**** | |
| None | 7 |
| 5-ASA | 21 |
| Immunomodulators | 28 |
| Biological agents | 16 |
| ***Surgical history*** | |
| None | 34 |
| 1 operation | 11 |

| | | |
|---|---|---|
| 2 operations | 8 | |

| | 1. CPM | 2. Global Motility Mean | 3. Global Motility Variance |
|---|---|---|---|
| fC | R = -0.22, P = 0.1 | R = -0.09, P = 0.51 | R = -0.33, P = 0.015* |
| HBI | R = 0.1, P = 0.46 | R = 0.06, P = 0.68 | R = -0.45, P <0.001* |

**Table 1** Summary of patient demographics.

* None = no CD specific medication, 5-ASA = 5-ASA medication alone, Immunomodulators = Immunomodulators including Methotrexate, Azathioprine & 6-Mercaptopurine) & Biological agents = biologics used alone or in conjunction with other agents.

| Metric | Median | Min | Max |
|---|---|---|---|
| 1-Mean CPM | 2 | 0.5 | 3.5 |
| 2- Global Motility Mean | 0.33 | 0.18 | 0.51 |
| 3. Global Motility Variance | 0.01 | 0.0014 | 0.0338 |
| CALP | 336 | 0 | 1280 |
| HBI | 3 | 0 | 16 |
| *Wellbeing* | *1* | *0* | *4* |
| *Abdominal pain* | *1* | *0* | *3* |
| *Liquid stool* | *1* | *0* | *13* |

**Table 2.** Median and range of motility and CD activity score values

**Table 3.** Correlation between CD activity endpoints and motility metrics.

| HBI Parameter | Correlation R |
|---|---|
| Wellbeing | *-0.4, p = 0.003** |
| Abdominal pain | *-0.27, p = 0.05** |
| Liquid stool | *-0.4, p = 0.0025** |
| Abdominal mass | *0.15, p = 0.3* |

**Table 4.** HBI indices correlated against global motility variance (R = correlation coefficient and p = corresponding significance value. * represents statistical significance <0.05).

| **Variable** | **Odds ratio (95% CI)** | **p value** |
|---|---|---|
| **Wellbeing (5 point scale, higher scores are worse)** | | |
| Age | 0.99 (0.95-1.03) | 0.64 |
| Sex | 0.29 (0.07-1.03) | 0.06 |
| Current smoker | 0.53 (0.05-4.21) | 0.57 |
| Previous surgery | 0.20 (0.03-1.02) | 0.07 |
| Medication | 0.86 (0.41-1.83) | 0.69 |
| BMI | 1.07 (0.90-1.26) | 0.46 |
| Disease Duration | 1.04 (0.91-1.19) | 0.56 |
| Faecal Calprotectin level | 1.00 (0.98-1.01) | 0.25 |
| *Global motility variance* | *0.19 (0.06-0.50)* | *<0.001* |
| **Abdominal Pain (4 point scale, higher scores are worse)** | | |
| Age | 0.98 (0.94-1.03) | 0.47 |
| Sex | 0.25 (0.06-1.00) | 0.06 |
| *Current smoker* | *0.06 (0.002-0.60)* | *0.04* |
| Previous surgery | 0.23 (0.04-1.25) | 0.11 |

| | | |
|---|---|---|
| Medication | 0.83 (0.38-1.88) | 0.65 |
| *BMI* | *1.20 (1.03-1.42)* | *0.03* |
| Disease Duration | 1.00 (0.87-1.15) | 0.98 |
| Faecal Calprotectin level | 1.00 (0.97-1.03) | 0.70 |
| *Global motility variance* | *0.26 (0.08-0.67)* | *0.004* |
| **Number of diarrhoeal stools** | **Incidence rate ratio (95% CI)** | **p value** |
| Age | 1.00 (0.98-1.03) | 0.71 |
| *Sex* | *0.24 (0.23-0.44)* | *<0.001* |
| Current smoker | 0.66 (0.002-0.60) | 0.43 |
| Previous surgery | 1.89 (0.04-1.25) | 0.12 |
| Medication | 1.08 (0.38-1.88) | 0.67 |
| BMI | 1.04 (1.03-1.42) | 0.35 |
| *Disease Duration* | *0.92 (0.87-1.15)* | *0.01* |
| Faecal Calprotectin level | 1.00 (1.00-1.01) | 0.07 |
| *Global motility variance* | *0.39 (0.23-0.61)* | *<0.0001* |

**Table 5** Relationship between HBI components of wellbeing, abdominal pain and number of diarrheal stools/day and demographic, clinical and motility variables, derived by ordinal logistic or negative binomial regression and expressed as odds ratios or incidence rate ratios respectively. Baseline categories for categorical variables as follows: sex = female, smoker = non-smoker, previous surgery = no prior surgery, medication (0 = no medication, 1= 5-ASA, 2 = Immunomodulators, 3 = immunologics. Significant results are shown in italics.

| | **1.5 T Siemens Avanto** | | **3T Philips Achieva** | |
|---|---|---|---|---|
| | Motility | Anatomical | Motility | Anatomical |
| *Sequence name* | TrueFISP | HASTE | BTFE | HASTE |
| *Plane* | Coronal | coronal/axial | coronal | coronal/axial |
| *Field of view (mm)* | Variable | Variable | Variable | Variable |
| *No. Slices* | 20 | 20/26 | 20 | 40/45 |

| | | | | |
|---|---|---|---|---|
| *Stacks* | 6-16 | 1/4 | 6-15 | 1/2 |
| *Repetition time (ms)* | 3.85 | 1,200/800 | 1.96 | 517/1450 |
| *Echo time (ms)* | 1.91 | 86/86 | 0.98 | 65/70 |
| *Image matrix* | 256 x 184 | 256x195 | 200 x 167 | 526x199/288x231 |
| *Slice thickness (mm)* | 10 | 4/4 | 10 | 7/4 |
| *Slice gap (mm)* | 10 | 5.2/5.4 | 10 | 8/5 |
| *Averages* | 1 | 1 | 1 | 1 |
| *Flip angle* | 61 | 50 | 45 | 90 |

**Appendix 1.** Motility sequences at the two field strengths along with the anatomical sequences used to identify diseased segments of bowel.