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Detection of Liver Injury in IBD Using Transient Elastography

L.W.Y Thin (FRACP)\textsuperscript{1,3}, Lawrance IC (PhD)\textsuperscript{1,2,3}, Spilsbury K (PhD)\textsuperscript{4}, Kava J\textsuperscript{3}, Olynyk J.K (MD)\textsuperscript{3,5,6}

\textsuperscript{1}Centre for Inflammatory Bowel Diseases, Fremantle Hospital, Fremantle, Western Australia.
\textsuperscript{2}University Department of Medicine and Pharmacology, University of Western Australia, Fremantle Hospital, Fremantle, Western Australia.
\textsuperscript{3}Department of Gastroenterology, Fremantle Hospital, Fremantle, Western Australia.
\textsuperscript{4}Centre for Population Health Research, Curtin University, Bentley, Western Australia.
\textsuperscript{5}Curtin Health Innovation Research Institute, Curtin University, Bentley, Western Australia, Australia.
\textsuperscript{6}Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, Western Australia, Australia.

**Running Title:** Transient elastography in IBD

**Address for correspondence and reprint requests:**

Corresponding Author:
Lena Thin
Level 5, T Block
Fremantle Hospital
Alma Street
Fremantle
6059, WA
Australia
ph 618 9431 2698
Fax 618 9431 3160
e-mail lenathin@gmail.com
Abstract:

Background: Up to 5% of inflammatory bowel disease (IBD) patients are thought to have clinically significant liver disease due to multifactorial causes, however, this figure may be an underestimate due to reliance on abnormal liver tests (LTs) and/or liver biopsies.

Aims: Our aim was to evaluate the prevalence of clinically significant liver disease in IBD patients as defined by an increased liver stiffness measurement (LSM) ≥8kPa using transient elastography (TE).

Methods: 110 IBD patients, and 55 non-IBD control subjects, had their LSM recorded using FibroScan® (EchoSense, Paris, France) by a single blinded operator trained in TE.

Results: 71 Crohn's disease and 39 ulcerative colitis subjects were included. All demographic variables were similar between the IBD and control groups apart from a significantly higher proportion of IBD patients who smoked (17.3% vs 3.6%, $P=0.013$). Seven IBD patients (6.4%) had an LSM over 8kPa and 3 had persistently elevated LSMs 6 months later. One patient had compensated cirrhosis. No significant differences in overall LSM were observed between the IBD and control groups. Increased BMI and age, however, were independently associated with a higher LSM in the IBD but not in the control group ($P<0.001$ and 0.010 respectively).

Conclusion: Using TE, the prevalence of clinically significant liver disease in IBD patients is low. The association of increased BMI and age with increased LSM in IBD suggests fatty liver disease being the prevailing aetiology in these patients.

Key words: NAFLD, IBD, liver stiffness, transient elastography
Introduction.

Hepatobiliary disease is one of the most common extra-intestinal manifestations of inflammatory bowel disease (IBD) with the prevalence of deranged liver biochemistry in these patients ranging between 3 and 50%. These changes may be transient or related to IBD activity, fatty liver disease, primary sclerosing cholangitis (PSC), medications (thiopurines and methotrexate), nodular regenerative hyperplasia, autoimmune hepatitis, and cholelithiasis. Another concern is that the use, and then the withdrawal, of immunosuppressive medications may result in flaring of pre-existing chronic hepatitis B, while the use of corticosteroids may promote the development of, or exacerbate, underlying non-alcoholic fatty liver disease (NAFLD). Finally, the anti-TNFα agents, whilst efficacious in combating gut mucosal inflammation, are hepatotoxic in some patients.

It is estimated that approximately 5% of adult patients with IBD will develop clinically significant liver disease, but a far larger proportion of patients will be noted as having abnormal liver biochemistries. The reliance on abnormal liver biochemistry to demonstrate liver injury, however, is flawed as the degree of biochemical derangement does not always correlate with the extent of liver injury and thus may result in either an over, or underestimation of the injury if used on its own. The addition of liver biopsies in these patients will improve the assessment of the liver, but are subject to sampling errors and are usually only performed in patients with markedly deranged liver tests. Patient acceptance of this test is often poor due to its invasiveness, pain and risk of morbidity. Thus, the true prevalence of clinically significant chronic liver disease in patients with IBD is not known and could be underestimated.
Transient elastography (TE) is a technique that utilises sound waves to assess liver stiffness. Liver stiffness measurements (LSMs) can be used to predict hepatic fibrosis and have been validated in patients with chronic hepatitis C where they are noted to be accurate predictors of advanced fibrosis and cirrhosis.\textsuperscript{14} This test is non-invasive, reproducible and not subject to the same sampling errors that can affect liver biopsies. More recently, TE was demonstrated to be accurate in detecting significant fibrosis (perisinusoidal and portal/periportal fibrosis, Metavir F2), advance fibrosis (septal or bridging fibrosis, Metavir F3) and cirrhosis (Metavir F4) in patients with NAFLD with area under receiver operator characteristic curve values of 0.84, 0.92 and 0.97 respectively.\textsuperscript{15} Its use has also been studied in cholestatic liver diseases\textsuperscript{14} and patients treated with methotrexate.\textsuperscript{16,17} The aim of this prospective study was, therefore, to identify the LSM characteristics of a cohort of IBD patients using FibroScan\textsuperscript{®} (Echosense, Paris France), the prevalence of clinically significant liver disease in this IBD cohort, and whether there are differences between the LSMs of the IBD and a non-IBD control group.
Methods

Study design and subjects

This was an observational prospective, cross-sectional study that recruited consecutive, consenting IBD patients between October 2011 and April 2012 from the Centre for Inflammatory Bowel Diseases, Fremantle Hospital, a specialised IBD unit. The study was reviewed and approved by the South Metropolitan Area Health Services Human Research Ethics Committee. All patients were 18 years or older with a diagnosis of IBD based on established clinical, endoscopic, radiological and histological criteria, and gave written informed consent prior to inclusion. Patient clinical details were collected including body mass index (BMI), history of diabetes mellitus, number of standard alcoholic drinks per week, smoking history, history of liver disease, Montreal classification, disease duration, current medications and IBD activity score at the time of the TE reading (Harvey Bradshaw Index (HBI), or partial Mayo score, for CD and UC respectively). Liver function tests were assessed within 1 month of the TE reading and all patients had their viral hepatitis serology and vaccination status checked as part of their routine clinical care in the IBD clinic. Random volunteers that did not have IBD, which included hospital staff and patient relatives, served as controls and had their TE readings compared with the IBD group. The ratio of non-IBD control to IBD subjects was 1:2.

Transient elastography.

The LSMs on all patients were performed by a single research nurse trained in TE using the FibroScan® (Echosens, Paris, France). LSMs were performed with the patient lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the transducer probe was covered with coupling gel and placed on the skin between the ribs at the level of the right lobe of the liver. A special obesity probe was used for subjects with a BMI greater
than 30kg/m². Only the results from subjects with 10 successful LSM acquisitions were included for analysis. The median value of these 10 readings represented the liver elastic modulus. The success rate was calculated by dividing the number of successful measurements by the total number of measurements; only those with a success rate of at least 60% were included in the study, as previously described. The operator was blinded to the patients’ clinical information.

Definitions

Based on prior experience in hepatitis C patients, a TE reading of greater than 8kPa was considered to represent a clinically significant level of fibrosis (≥F2 on the Metavir scale). The definitions for liver injury were derived from the International Consensus meeting recommendations organised under the auspices of the Council for International Organisations of Medical Sciences (CIOMS). “Abnormality of liver tests (LT)” was defined as an increase in AST, ALT, ALP, GGT or total bilirubin between N (upper limit of normal range) and 2N. “Liver injury” or “hepatotoxicity” was defined as an increase of over 2N in ALT. “Marked liver injury/ severe hepatotoxicity” was considered if the transaminases were greater than 5N.

Those patients with LTs >2N, or TE readings greater than 8kPa, were assessed for autoimmune (anti- smooth muscle antibody, anti- liver-kidney microsomal antibody, immunoglobulins, anti- mitochondrial antibody), viral (hepatitis B and C serology) and metabolic (caeruloplasmin, iron studies, alpha-1 antitrypsin deficiency) causes along with a hepato-biliary ultrasound. TE and LTs in these patients were then repeated 6 months after the first abnormal reading and if these were persistently abnormal, the patients were referred for hepatology review and consideration of a liver biopsy. Control subjects who were noted to have abnormal results were followed in a similar manner.
Statistical methods

Statistical tests were performed using Statistical Package for Social Sciences version 16 and STATA version 12. Due to non-normality and a tendency towards large differences in the variance of the continuous variables in this study (age, BMI, LSM and number of standard alcoholic drinks per week) the medians and interquartile range were used to summarise the central tendency by IBD group, although means and t-test p-values were also calculated. Categorical variables were summarized as proportions. Non-parametric Mann-Whitney U tests were performed to compare control and IBD group differences between continuous variables and chi-square test or Fisher’s exact test (when expected values < 5) on categorical variables. All statistical tests were two sided with a significance level of 0.05.

Multi-variable regression models were used to find factors associated with increased LSM values. Initially standard linear regression models were assessed but normality and constant variance (heteroscedasticity) assumptions were violated at the higher LSM values. A log transformation of the LSM values reduced these problems and to avoid having to back-transform coefficients, generalized linear models using a log link and Gaussian distribution were used to investigate the association. Purposeful backward stepwise model building involved including all variables with p-values ≤0.25 in univariate analyses and then removing variables one at a time until only those remaining had p<0.05. Plausible interaction terms were then tested amongst remaining and any dropped variables. Robust standard errors were used to account for any remaining heteroscedasticity.
Results
A total of 114 IBD patients and 59 non-IBD control patients underwent TE. 4 IBD patients (3.6%) and 4 non-IBD control subjects (7.2%) were subsequently excluded due to unsuccessful TE acquisitions. The baseline demographical and disease characteristics are presented in Table 1 and Table 2 respectively. There were no significant differences in the baseline characteristics between the two groups apart from a greater proportion of current cigarette smokers (>1 cigarette/day) in the IBD group compared to the control group (17.3% vs 3.6%, \( P=0.013 \)). There was a tendency towards the IBD group to have a higher BMI but this was not statistically significant.

Of the IBD group, approximately two thirds were Crohn’s disease (CD) patients (Table 2). The mean duration of disease in the IBD group overall was 12 years and the majority were on an immunosuppressing medication; azathioprine/6-MP (40.9%), methotrexate (1.8%), tacrolimus (2.7%)) or an anti-TNFα medication (infliximab; 7.3%, adalimumab; 18.2%). 75% of CD patients and 79.5% of UC patients were in remission at the time the TE reading was taken, defined as a HBI of \( \leq 4 \) and partial Mayo score of \( \leq 2 \) respectively. The mean HBI score in CD patients was 2.7 ± 4.1, and partial mayo score in UC patients was 1.4 ± 2.4.

No patients in the control group had a history of liver disease, while 5 IBD patients had a known history, 3 with NAFLD and 2 with PSC. Of these 5 patients, 1 patient with NAFLD had an abnormal TE reading (8.6kPa) and normal LTs while 1 patient with PSC had cholestatic LTs and a normal TE reading. The other 3 patients had normal TE readings and LTs. There were 2 IBD patients that were taking methotrexate and had normal LTs and TE readings.
Difference in LSM between IBD and control groups

There was no statistically significant difference in the median LSM values between the control and IBD groups (4.5kPa; IQR 3.9-5.6kPa vs 4.7kPa; IQR 4-6kPa, \( P=0.626 \) Table 1). 7 IBD patients (6.4%) had a TE reading \( \geq 8 \)kPa compared to none of the controls. All 7 patients had normal LTs, normal autoimmune, viral and metabolic blood tests for hepatological workup and two had sonographic features of a fatty liver. 3 of the 7 patients had persistently elevated TE readings when rechecked six months later and this was associated with weight gain (Table 3), while the other 4 had normalised their LSMs and this was accompanied by weight loss. One of the patients with a persistently elevated TE reading of 12.1kPa (Table 3, case #7) was considered to have compensated cirrhosis with a low platelet count, coarsened echo texture and splenomegaly on ultrasound. This patient was referred to hepatology clinic for review, however no liver biopsy has been undertaken due to poor patient acceptance of the procedural risks and the likelihood of NAFLD/NASH being the underlying cause.

Interaction between LSM, age and BMI in IBD vs non-IBD control groups.

Further investigation demonstrated that while the overall LSM values were similar in both groups, LSM values within the control and IBD groups varied significantly with age and BMI. Regression analyses identified an association between increased LSM and IBD that was modified by patient age and BMI (Table 4). There was a trend of an increase in mean LSM with increasing age but only in patients with IBD. IBD patients aged \( \geq 60 \) years had a mean LSM 2.1 kPa higher than IBD patients aged \( <40 \) years. In contrast, there was no increase in mean LSM with age in the control group; instead there was some evidence of small decrease in mean LSM with increasing age. The association of LSM with IBD was also modified by patient BMI. An increase in BMI was associated with an increased mean LSM
value in IBD patients. IBD patients with a BMI >30kg/m² had mean LSM values 3.5 kPa higher than IBD patients of normal weight or lower. There was no statistically significant effect of BMI on LSM values in the control group.

Effect of anti-TNFα agents on LSM

There were 28 patients (25.5%) in this study on an anti-TNFα medication. After controlling for IBD, BMI and age, IBD patients who were being treated with an anti-TNFα agent had a lower mean LSM compared to those who were not (4.5 kPa, 95% CI 4.1-5.0 vs 5.2 kPa, 95%CI 4.9-5.5; P=0.048). There was no significant difference in the proportion of anti-TNFα-treated IBD patients who were in disease remission (85.7% vs 73.2%, P=0.2), or on corticosteroid therapy (10.7% vs 14.6%, P=0.6) compared to those not on an anti-TNFα agent.

Gender, diabetes status, IBD disease duration and disease activity, corticosteroid use, immunomodulator treatment, smoking, alcohol consumption and history of liver disease were not associated with significant differences in LSM values and were removed from the regression model.

To investigate whether the observed association of IBD and LSM could be attributed to the underlying disease, a regression model that specified the IBD subtype as CD or UC was constructed. A similar model with age and BMI interaction terms indicated that most of the observed increase in LSM with increasing BMI observed earlier in IBD patients was from CD patients (Table 5). For the control group and for patients with UC there was no evidence in this study that increasing BMI was associated with higher LSMs. As only a third of all IBD patients had UC however, this lack of an association could be the result of inadequate
power. There was evidence that the association of increasing LSM with increasing age in IBD patients was seen in both patients with UC and CD, however a larger study would be needed to confirm these trends.

*Patients with abnormal LT but normal LSMs.*

Four patients with normal LSMs had evidence of mild liver injury (LT> 2N), although none had LTs which exceeded 3N. The aetiologies given in the clinical history and after hepatological workup were, thiopurine metabolite shunting in 1 patient, excessive alcohol use in 1 patient and NAFLD/NASH in 2 patients. The thiopurine shunter had a 6MMP level of 8470 pmol/8x10^8 RBC which decreased to <500 pmol/8x10^8 RBC accompanied by a normalisation of transaminases on addition of allopurinol. The other 3 patients had persistently elevated transaminases that were <2N on follow up and were advised to lose weight/ decrease alcohol use.
Discussion.

Few studies have explored the liver health of the IBD population using TE and the studies that are available, have examined only CD patients treated with methotrexate.\textsuperscript{13,16,19} These studies have shown that the prevalence of liver fibrosis from methotrexate itself is low and that the aetiology for any raised LT or TE reading is more likely due to NAFLD or excessive alcohol use. As hepatobiliary complications in IBD patients are not uncommon and heterogeneous in aetiology, our aim in this study, was to characterise the LSM characteristics of a cohort of IBD patients and evaluate the prevalence of clinically significant liver disease from any cause as defined by a TE reading of $\geq8$ kPa.

The definition of ‘significant fibrosis (Metavir F2)’ ‘advanced fibrosis’ (Metavir F3) and ‘cirrhosis’ (Metavir F4) have been evaluated in many studies using FibroScan\textsuperscript{®} (Echosense, Paris, France) with the findings most recognised in hepatitis C patients. Work has also been performed on NAFLD/NASH patients which have demonstrated comparable accuracy that was not compromised by BMI or degree of steatosis.\textsuperscript{15} Cut off levels for each category of fibrosis is variable, however, most work performed on hepatitis C cases have shown that Metavir F2, F3 and F4 levels of fibrosis correspond to a TE values of 7.1-8.8kPa, 9.5-9.6 kPa, and 12.5 to14.6 kPa respectively based on a comprehensive review.\textsuperscript{14} Accordingly, in this study clinically significant liver disease was defined as F2, which was to be a TE reading of $\geq8$ kPa.

This study demonstrated no significant differences in the overall LSM between the IBD patients and controls. The prevalence of clinically significant liver disease in IBD was noted to be low (6.4%) and the 7 patients were thought to have NAFLD following a normal hepatological work up, the presence of an elevated BMI and/or ultrasonographic findings of a
fatty liver. Only 3 patients had a persistently elevated LSM after 6 months of follow-up associated with a corresponding weight gain with 1 patient that was suspected to having compensated cirrhosis. The low numbers of IBD patients with potentially significant liver disease is reassuring and is consistent with what is known in the literature.\textsuperscript{10}

Although the LSMs of IBD patients did not significantly differ between IBD and control patients, a higher BMI and increased age were both significantly associated with a higher LSM in the IBD group, a finding that was not observed in the control group. This lack of association in the control group may be due to the “healthy worker effect” as this group consisted of hospital staff such as medical students, doctors and nurses who may be healthier individuals that are not entirely representative of the general population from which similar trends probably exist. The association between increased BMI and LSM in the IBD group combined with the results of the complete hepatological workup suggests that NAFLD is the likely underlying aetiology of the increased LSM. Increased age being associated with higher LSMs may be explained by the higher likelihood of metabolic syndrome in older individuals, contributing to NALFD. We did not, however, formally seek to identify or measure metabolic risk factors in this study apart from the presence of diabetes mellitus.

The trend observed for an increased LSM in IBD patients with a higher BMI was only observed in the CD subgroup, but the reason may be due to an inadequate sample size of UC patients. It is, however, well-known that smoking plays an important role in CD and a significant proportion of our CD cohort smoked. This may predispose these patients to NAFLD as one study investigating a large cohort of NALFD patients demonstrated that a >10 smoking pack years was an independent predictor of progression to advance fibrosis, potentially mediated through an increase in insulin resistance.\textsuperscript{20}
One quarter of the total IBD group was on an anti-TNFα agent, which was associated with a lower LSM value. In this cohort, being on an anti-TNFα medication was not significantly associated with increased proportions of patients in disease remission, or on corticosteroid free regimens, which might have otherwise explained a lower risk of metabolic syndrome and NAFLD. Cumulative corticosteroid dose however, which may have a stronger link with NAFLD, was not measured in this study and may be lower in those patients on an anti-TNFα agent due to better disease control. Another possible explanation lies in the potential biological effects of anti-TNFα agents on hepatic inflammation and fibrogenesis. Although there have been documented hepatotoxic drug-induced, autoimmune like reactions from anti-TNFα medications, these agents have also been shown to improve necro-inflammatory changes in alcoholic hepatitis and in vitro models of NASH, due to the up regulation of TNFα in these disease processes. The possible protective value of anti-TNFα medications requires further investigation in larger studies.

An additional potential limitation of the study might relate to the smaller sample size in subgroups which reduced the ability to explore any further relationships. A post-hoc power calculation indicated that this study would have had 90% power to detect a difference of 0.9 in mean LSMs at a 0.05 significance level. This study was, therefore, underpowered to detect small changes in mean LSM values that may have been present. No liver biopsies were performed on any of the patients with either an elevated TE reading, repeated readings and/or those with abnormal LT’s. Poor patient acceptability, lack of strength for an indication and lack of influence on clinical management were the reasons given to decline a liver biopsy. This did not detract, however, from achieving the aim of this study, which was to apply a validated modality liver fibrosis assessment on a group of IBD patients to characterise the LSMs in this group.
In conclusion this study demonstrated that the prevalence of potentially clinically significant liver disease using TE, in an IBD population is low and that any prevailing liver abnormality is most likely secondary to NAFLD. Optimisation of metabolic risk factors, including emphasis on smoking cessation and minimisation of corticosteroid use, should continue to be important priorities in the management of the IBD patients.

Acknowledgement
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References


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<sup>a</sup>BMI= Body mass index (kg/m²)  
<sup>b</sup>LSM= Liver stiffness measurement
Table 2 Disease Characteristics of IBD patients.

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<th></th>
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<th>UC n = 39</th>
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<tr>
<td>A3</td>
<td>14 (19.7)</td>
<td>9 (23.1)</td>
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<td><strong>Location n= (%)</strong></td>
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<td>B2</td>
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<td><strong>Disease duration mean yrs±SD</strong></td>
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<td><strong>Smokers n= (%)</strong></td>
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<td><strong>Medication use; n (%)</strong></td>
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<td>5-ASA</td>
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<td><strong>Mean Disease Activity scores (SD)</strong></td>
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<tr>
<td>CD (HBI)</td>
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<td>1.4 ± 2.4</td>
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<td><strong>Proportion in remission at TE reading n= (%)</strong></td>
<td>53 (75)</td>
<td>31 (79.5)</td>
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</table>

Abbreviations: HBI – Harvey Bradshaw index  

a3 patients used rectal 5ASA  
b1 patient used rectal steroids
Table 3. Cases with elevated LSM readings and repeat LSM reading with BMI taken 6 months later.

<table>
<thead>
<tr>
<th>Case No #</th>
<th>Baseline LSM reading</th>
<th>Baseline weight</th>
<th>Repeat LSM reading&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Repeat weight&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.9</td>
<td>81</td>
<td>10</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>21.1</td>
<td>87</td>
<td>6.4</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>8.6</td>
<td>85</td>
<td>8.0</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>10.2</td>
<td>122</td>
<td>6.5</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>9.4</td>
<td>92</td>
<td>6.7</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>8.6</td>
<td>74</td>
<td>6.4</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>15.1</td>
<td>86</td>
<td>12.1</td>
<td>89</td>
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</table>

<sup>1</sup> Repeat weight and LSM reading were performed 6 months after the first measurement.
Table 4: Factors associated with change in LSM values as estimated from a generalised linear model with robust standard errors.

<table>
<thead>
<tr>
<th></th>
<th>Δ mean LSM</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBD status within BMI categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>ref&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25-29</td>
<td>-0.33</td>
<td>-0.95 – 0.29</td>
<td>0.291</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>-0.19</td>
<td>-0.91 – 0.54</td>
<td>0.614</td>
</tr>
<tr>
<td><strong>IBD group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25-29</td>
<td>0.58</td>
<td>0.02 – 1.13</td>
<td><strong>0.044</strong></td>
</tr>
<tr>
<td>&gt;=30</td>
<td>3.48</td>
<td>1.49 – 5.46</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td><strong>Age group within IBD status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40-60 years</td>
<td>-0.26</td>
<td>-0.89 – 0.37</td>
<td>0.422</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>-0.75</td>
<td>-0.01 - -0.08</td>
<td><strong>0.028</strong></td>
</tr>
<tr>
<td><strong>IBD group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40-60 years</td>
<td>0.62</td>
<td>-0.01- 1.26</td>
<td><strong>0.053</strong></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>2.07</td>
<td>0.32 – 3.83</td>
<td><strong>0.020</strong></td>
</tr>
<tr>
<td><strong>Anti-TNF treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>- 0.63</td>
<td>-1.25 - -0.02</td>
<td><strong>0.043</strong></td>
</tr>
</tbody>
</table>

<sup>1</sup>Ref= Referent group.
Table 5. Factors associated with change in mean LSM score with IBD categorised into specific disease type as estimated from a generalised linear model with robust standard errors.

<table>
<thead>
<tr>
<th>BMI category within IBD disease type</th>
<th>Δ mean LSM</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25-29</td>
<td>-0.33</td>
<td>-0.95 – 0.29</td>
<td>0.291</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>-0.19</td>
<td>-0.91 – 0.54</td>
<td>0.614</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25-29</td>
<td>0.35</td>
<td>-0.59 – 1.28</td>
<td>0.467</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>3.98</td>
<td>1.97 – 6.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25-29</td>
<td>0.50</td>
<td>-0.38 – 1.38</td>
<td>0.268</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>1.68</td>
<td>-0.57 – 3.94</td>
<td>0.143</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group within IBD disease type</th>
<th>Δ mean LSM</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40-60 years</td>
<td>-0.26</td>
<td>-0.89 – 0.37</td>
<td>0.422</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>-0.75</td>
<td>-1.41 – -0.08</td>
<td>0.028</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40-60 years</td>
<td>0.55</td>
<td>-0.47 – 1.57</td>
<td>0.292</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>2.77</td>
<td>0.70 – 4.84</td>
<td>0.009</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40-60 years</td>
<td>0.96</td>
<td>0.04 –1.88</td>
<td>0.041</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>0.87</td>
<td>-0.98 – 2.42</td>
<td>0.247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-TNF treatment</th>
<th>Δ mean LSM</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>- 0.72</td>
<td>-1.40 – -0.05</td>
<td>0.037</td>
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</table>

¹Ref = referent group