



UNIVERSITY OF LEEDS

This is a repository copy of *Depression Is Associated With Subjective Measures of Crohn's Disease Activity During Longitudinal Follow-up*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/104266/>

Version: Accepted Version

Article:

Gracie, DJ and Ford, AC orcid.org/0000-0001-6371-4359 (2016) Depression Is Associated With Subjective Measures of Crohn's Disease Activity During Longitudinal Follow-up. *Gastroenterology*, 151 (4). pp. 762-763. ISSN 0016-5085

<https://doi.org/10.1053/j.gastro.2016.08.037>

© 2016, Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International
<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Reuse

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Title: Depression is associated with subjective measures of Crohn's disease activity during longitudinal follow-up.

Comment on: Gaines L, Slaughter J, Horst S et al. Association Between Affective-Cognitive Symptoms of Depression and Exacerbation of Crohn's Disease. *Am J Gastroenterol.* 2016; doi: 10.1038/ajg.2016.98

Authors: David J Gracie^{1,2}, Alexander C Ford^{1,2}

¹Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

²Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

Correspondence: Dr. David J Gracie

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: djgracie1982@doctors.org.uk

Telephone: +441132684963

Facsimile: +441132429722

Summary

Crohn's disease (CD) is associated with a higher prevalence of depression than is observed in the general population. The presence of such psychological co-morbidity may affect disease outcomes in CD, with some studies suggesting the presence of depression increases risk of flares of disease activity (*Am J Gastroenterol* 2010;105:1994-2002).

The authors methodology included a longitudinal follow-up design, to investigate the association between depression and disease activity in CD. 2,144 patients with self-reported CD completed an online survey at baseline and 12 months, including the National Institutes of Health Patient Reported Measurement Information Systems questionnaire (PROMIS) as a measure of depression, and the short Crohn's Disease Activity Index questionnaire (SCDAI), as a measure of CD activity. PROMIS depression scores, based on responses to four Likert-scale items, were converted into standardized scores (t-score). Disease activity was modelled as both a continuous SCAI t-score and a binary outcome with active disease defined as a t-score >150. Linear or logistic regression was used to model continuous scores or binary outcomes respectively, from which the expected change in mean SCAI at 12 months, as well as odds ratios (ORs) of having active disease (SCDAI >150), were calculated per 10-point increase in depression t-score over 12 months. The hypothesis was that CD patients experiencing affective-cognitive symptoms of depression at baseline would be more likely to report active CD 12 months later, and that these depressive symptoms would be associated with increased odds of hospitalization, surgery, and biologics usage.

The results demonstrated that, after adjusting for baseline SCAI score, there was a significant association between baseline depression t-score and 12 month follow-up SCAI score using linear regression models ($P < 0.001$). A 10-point increase in baseline depression t-score from 55 to 65 was associated with an 18.6 point increase in SCAI (95% confidence interval (CI) 11.5-25.6), compared with a 6.9 point increase (95% CI 2.4-11.4) in SCAI

score at 12 months with a baseline increase from 45 to 55, suggesting an association between increasing depressive burden and SCDAI scores over the 12 months. Similar results were found in logistic regression analyses, where a significant increase in the odds per 10-point increase in baseline depression t-score was observed for active disease (OR = 1.21; 95% CI 1.07-1.36), hospitalization (OR = 1.26; 95% CI 1.06-1.49) but not surgery (OR = 0.94; 95% CI 0.72-1.22) or biologics usage (OR = 0.91; 95% CI 0.78-1.08).

The authors concluded that depressive symptoms were significantly associated with risk of exacerbation of CD and hospitalization.

Commentary:

CD is a chronic inflammatory bowel disease (IBD) of uncertain etiology. The natural history of the disease is that of quiescence, interspersed with periodic flare-ups of disease activity. Several factors have been implicated in the development of active disease, including a pro-inflammatory microbiome and dysregulation of the enteric nervous system. In keeping with other chronic medical disorders, the prevalence of psychological co-morbidity in CD is relatively high (Am J Gastroenterol. 2008;103:1989-97). Triggers for the development of depression in IBD, including both aggressive and active disease, suggest the existence of a link between gut and brain (Aliment Pharmacol Ther. 2014;39:802-10).

These brain-gut interactions have been studied extensively in irritable bowel syndrome (IBS), where a bi-directional relationship between the presence of symptoms and psychological co-morbidity has been described (Gut. 2012;61(9):1284-90). However, evidence to support the existence of such a relationship in CD is, to date, lacking. Further examination of the relationship between brain and gut in IBD is clinically relevant, particularly if the presence of depression is associated with adverse disease outcomes, as this may provide a mandate for clinical trials of interventions such as psychological therapy or anti-depressants in the management of IBD.

Gaines et al. report the effect of depression on the development of self-reported flare of disease activity in a large cohort of CD patients, after 12 months of follow-up. Their findings suggest that increasing severity of depression is associated with greater odds of developing self-reported disease activity or hospitalization, but not increased requirement for surgery or biologics. Although these findings suggest depression may influence the natural history of CD, there are several limitations which question the strength of this interaction, based on these findings alone. The association between self-reported disease activity, using

clinical disease activity indices such as the SCDAI or Harvey Bradshaw Index, and objective measures of IBD activity is poor, particularly in CD, but has been shown to correlate with perceived stress, somatization, and the presence of IBS-type symptoms (Am J Gastroenterol 2016;111:541-51) (Am J Gastroenterol 2015;110:1001-12).

The lack of an objective measure of intestinal inflammation in this study means that patients with quiescent disease with co-existent IBS-type symptoms, which may affect >40% of individuals with CD (Am J Gastroenterol. 2012;107:1474-82), and is independently associated with psychological co-morbidity (Am J Gastroenterol. 2016;111:93-104), may have been misclassified as having 'true' inflammatory activity based on clinical indices, resulting in an overestimation of the effect of depression on CD activity. Indeed, the findings of a recent cross-sectional survey combining clinical disease activity indices, Rome III-defined IBS, and fecal calprotectin as an objective measure of intestinal inflammation, suggest that the prevalence and severity of psychological co-morbidity in CD patients with IBS-type symptoms in the absence of mucosal inflammation is similar to those reporting gastrointestinal symptoms with objective evidence of mucosal inflammation (Clin Gastroenterol Hepatol 2016;doi:10.1016/j.cgh.2016.05.012.).

Despite this, the assertion that depression is associated with increased symptom reporting is clinically relevant in itself, particularly as it is the presence or absence of these symptoms that forms the mainstay of disease activity assessment and decision-making in the outpatient setting. It is likely, therefore, that the heightened symptom reporting observed in such patients will be associated with greater utilization of healthcare resources, at substantial cost. Therefore, these data support the requirement for a shift in IBD management strategy away from one focussed solely on addressing the severity of inflammatory burden, towards an integrated model of care encompassing assessment and management of both physical and psychological health, as has been advocated previously (Am J Gastroenterol 2010;105:1796-

8). Furthermore, evidence to support increased symptom reporting in patients with depression suggests clinical trials of pharmacological and psychological therapies aimed at managing co-existent psychological co-morbidity in CD is warranted, independent of any potential association of such symptoms with biochemical disease activity.

In conclusion, this longitudinal follow-up study demonstrates that antecedent affective-cognitive symptoms of depression are associated with subsequent development of gastrointestinal symptoms in CD. However, in the absence of an objective measure of intestinal inflammation, these findings do not support the conclusion that psychological co-morbidity is related to the development of active inflammation in CD. Disease activity assessment in CD is complex and, when used in isolation, clinical disease activity indices and patient reported outcome measures should be interpreted with caution. Psychological co-morbidity in CD is common, but its impact on the natural history of CD remains uncertain. Prospective, longitudinal studies examining the relationship between depression and mucosal inflammation are required to delineate this matter further.