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SYMPTOMS OF DEPRESSION AND ANXIETY ARE INDEPENDENTLY ASSOCIATED WITH CLINICAL RECURRENCE IN INFLAMMATORY BOWEL DISEASE

Short title: Depression and IBD activity over time

Word count: 2,580

Antonina Mikočka-Walus, PhD^{1,2,3*}; Valerie Pittet, PhD⁴; Jean-Benoit Rossel, PhD⁴; Roland von Känel, MD^{5,6,7} and the Swiss IBD cohort study group

¹Department of Health Sciences, University of York, York, United Kingdom

²School of Psychology, University of Adelaide, Adelaide, Australia

³Foundation Brocher, Geneva, Switzerland

⁴Health Care Evaluation Unit, Institute of Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland

⁵Department of Clinical Research, University of Bern, Switzerland

⁶Department of Neurology, Inselspital, Bern University Hospital, Switzerland

⁷Department of Psychosomatic Medicine, Clinic Barmelweid, Barmelweid, Switzerland

* Corresponding author

Mental Health and Addiction Research Group

Department of Health Sciences

University of York

Heslington

York YO10 5DD

Tel: 0044 1904 32 1521

Email: antonina.mikocka-walus@york.ac.uk

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ABSTRACT

Background and aims: This study aimed to examine the relationship between symptoms of depression and anxiety and clinical recurrence in a large IBD cohort, by taking into account the evolution of depression and anxiety over time.

Methods: This is a prospective cohort study using data from participants included in the Swiss IBD cohort from 2006 till 2015. Data on depression and anxiety symptoms were collected using the Hospital Anxiety and Depression Scale (HADS). The relationship between depression and anxiety scores and the clinical recurrence was analyzed using survival-time techniques.

Results: A total of 2,007 participants, 56% with Crohn's disease, 48% male, were included in the analysis. There was a significant association between symptoms of depression and clinical recurrence over time (all IBD $p=0.000001$; CD $p=0.0007$; UC $p=0.005$). There was also a significant relationship between symptoms of anxiety and clinical recurrence over time in the whole sample ($p=0.0014$) and in the CD participants ($p=0.031$), but not in the UC participants ($p=0.066$).

Conclusions: Screening for clinically relevant levels of depression and anxiety and referring for psychological/psychiatric treatment, as part of standard IBD care, seems warranted.

Keywords: anxiety; depression; inflammatory bowel disease; prospective

INTRODUCTION

Inflammatory bowel disease (IBD), of which Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC) are subtypes, is a chronic relapsing gastrointestinal condition with etiology involving a deregulated immune response to intestinal microbiome, triggered by environmental factors, in those with a genetic susceptibility. There are over 2.2 million people living with IBD in Europe,(1) 12,000 in Switzerland alone,(2) and its incidence is on the rise.(3) The overall annual cost of IBD to European healthcare systems is estimated to be EUR4.6-5.6 billion.(3)

IBD is associated with a clinically highly relevant and significant psychosocial burden.(4-9) A large Canadian population-based study reported the rates of depression in IBD to be three times higher than in the healthy population.(9) Symptoms of depression and anxiety have been linked to more severe IBD symptoms and more frequent IBD flares,(8) increased hospitalisation rates,(10) and lower compliance with treatment.(11) However, the relationship of depression and anxiety with disease activity in IBD has been controversial,(12) with no causal link established to date. Although some reviews have been published on the relationship between psychological factors and disease activity,(13-15) none to date has been systematic.

Our recent search of MEDLINE, Embase, CINAHL, PsychINFO and Web of Science, for the purpose of this study, identified 12 prospective studies on depression and anxiety in IBD (studies on stress only were excluded), with samples varying from 18 to 388(8, 16-26) and an observation period of up to 37 months. Seven of these studies (n=978) observed a significant positive relationship between symptoms of depression and anxiety and disease activity(8, 16, 19-21, 23, 24) while five (n=336) did not make this observation.(17, 18, 22, 25, 26) The

conflicting evidence in these studies may result from the observation periods that were too short (only in five studies the follow up exceeded one year) and small and unrepresentative samples (six studies with $n < 100$), but also from different definitions and measures of depression and anxiety (only one study(16) used clinical interviews and thus provided data on the diagnosis of depression and anxiety rather than symptoms only), and measures of disease activity. Studies addressing these limitations of the previous literature are needed to inform current research and practice in IBD.

The Swiss IBD cohort (SIBDC) offers an ideal setting for conducting a comprehensive study on a large IBD sample over a long period of time, allowing for an observation of the natural course of IBD. The present study thus aimed to examine the relationship between symptoms of depression and anxiety and clinical recurrence in a large IBD cohort, by taking into account the evolution of depression and anxiety over time. The study examined the following hypothesis: There is a significant relationship between depression and anxiety symptoms and clinical recurrence over time. Given the inconclusive results across previous studies, we did not specify the direction of this relationship.

MATERIALS AND METHODS

Design and setting

This is a prospective cohort study using data from participants who had been included in the SIBDC between 2006 and 2015.(2) Participants were included through their treating gastroenterologist, located in Swiss university hospitals, regional hospitals and private practices. Clinical and treatment data were collected during the enrolment and yearly follow-up medical visits; in addition, participants were receiving self-administered questionnaires (at

enrolment and on a yearly basis) comprising socio-demographic and psychosocial data, to be completed at home. The study reporting followed the STROBE Statement.

Selection criteria

All adult patients who were enrolled in the SIBDC (to be included, patients must have a diagnosis established at least 4 months prior to inclusion or have had at least one recurrence of symptoms), who completed the baseline patient self-reported questionnaire and the one year follow-up medical visit, were included. Pregnant patients and those with missing data on depression and anxiety scores were excluded.

Measures

To minimize the assessment bias and optimize data quality of the registry, gastroenterologists and study nurses were asked to clarify inconclusive data for information collected from patient charts (clinical and treatment characteristics).

Depression and anxiety symptoms were measured using the Hospital Anxiety and Depression Scale (HADS). The HADS is a self-assessment mood scale developed for medical outpatients(27) containing 14 questions graded on a 4-point Likert scale, with subscales of anxiety and depression, with a sum score ranging from 0 to 21 for each, and a cut-off value of >7 on either of the two subscales. The scores of 0-7 are considered normal; 8-10 are indicative of mild anxiety / depression symptoms; 11-14 are indicative of moderate anxiety / depression symptoms; 15-21 are indicative of severe anxiety / depression symptoms.

Disease activity measures included the widely used Crohn's Disease Activity Index (CDAI)(28) and the Modified Truelove and Witts Severity Index (MTWAI),(29, 30) as appropriate. These were collected by the clinicians.

Outcome measure

We were interested in the relationship between the symptoms of depression and anxiety and a clinical recurrence, as a measure of outcome. The outcome was constructed by taking account of the following variables: disease activity, flare events or worsening of the disease (established by physicians as part of their assessment of the patient's overall disease activity), fistulas and stenosis, anal fissure, abscess, IBD surgery (including any type of resection, colectomy, ileostomy, colostomy), and intake of steroids or biologics. The endpoint was reached when any of these events occurred. Each participant started with a value of 0 at baseline, and this value became 1 when an event occurred. If a participant had already experienced the outcome (e.g. a fistula) at baseline, we were then interested in the appearance of the next event. We were interested in the time of the first appearance of a clinical recurrence event after enrolment. For each participant, we defined a time interval $(t_n, t_{n+1}]$ where t_n corresponded to the time of the n^{th} visit. In this situation, we knew that no relevant event had occurred before t_n , but at least one clinical recurrence event from the list above occurred between t_n and t_{n+1} .

Data Analysis

The composite outcome measure (clinical recurrence) was a 0/1 variable, which was analyzed using survival-time techniques. For each participant, the time between 0 and t_{n+1} was split in several smaller subintervals, according to their depression and anxiety levels. In each subinterval, depression and anxiety were assumed to be constant. The non-parametric approach of Kaplan-Meier curves with standard survival techniques, where events occurred

exactly at t_{n+1} , was applied. The obtained survival curves were compared using the log-rank test, in order to quantify differences in survival probability (event-free probability) between participants with and without depression and anxiety. Missing or invalid information on the variables of interest resulted in exclusion of the respective case from analysis.

ETHICAL CONSIDERATIONS

The ethical committees of all Cantons where participants were included approved the Swiss IBD Cohort Study, and all the participants were enrolled after providing written informed consent.

RESULTS

Descriptive statistics

Of the 2,886 participants registered in the Swiss IBD cohort, 879 did not meet the inclusion criteria for the present study and were excluded. In particular, after excluding pregnant patients, 2,870 (99.4%) cases remained in the study. After excluding those who did not answer the questionnaire, 2,321 (80.4%) cases remained in the study. After excluding patients for whom depression and anxiety levels were unknown, 2,289 (79.3%) remained in the study, and finally, after excluding participants that were lost to follow-up (participants are considered lost-to-follow-up if they did not come for a medical visit / did not reply to a patient questionnaire for ≥ 18 months) after the enrollment, 2,007 (69.5%) remained in the study and these 2,007 participants were thus included in the analysis.

Overall, 55.9% participants had CD, and 48.3% were males (CD: 45.6%, UC: 51.8%). At baseline, median age was 40.5 years, median disease duration was 7.2 years, and 20.2% of participants had a depression score while 37.5% had an anxiety score above the cut-off value

(>7) (Table 1). There was no difference between the sexes in depression at baseline (200 (20.6%) males versus 205 (19.8%) females, $p=0.635$). However, there was a significant difference in anxiety at baseline between the sexes, with 304 (31.3%) male participants versus 448 (43.2%) female participants anxious ($p<0.001$). There was no significant association between the CDAI score, anxiety or depression at baseline ($p=0.221$ and $p=0.266$, respectively). Similarly, there was no association between the MTWAI score, anxiety or depression ($p=0.167$ and $p=0.288$, respectively).

Symptoms of depression and anxiety and clinical recurrence over time

Figure 1 and Figure 2 present the Kaplan-Meier curves of the association between depression symptoms, anxiety symptoms and clinical recurrence. There was a strong and statistically significant relationship between depression and clinical recurrence over time (all IBD $p=0.000001$; CD $p=0.0007$; UC $p=0.005$). However, this relationship was less obvious for anxiety symptoms. The relationship between anxiety and clinical recurrence over time was observable in the whole sample ($p=0.0014$) and in the CD participants alone ($p=0.031$), but not in the UC participants ($p=0.066$). These results indicated that those IBD participants who reported clinically relevant symptoms of depression or anxiety (HADS score >7) had shorter time to a clinical recurrence event than the participants without depression or anxiety symptoms. When sex was factored in the Kaplan-Meier curves and a comparison conducted using a log-rank test, no significant difference was detected ($p>0.05$), indicating that the relationship between depression and clinical recurrence or anxiety and clinical recurrence is not influenced by sex.

Exploring particular components of the composite outcome responsible for the effect, using the Kaplan-Meier curves, we observed that there was a statistically significant relationship

between depression and fistula in CD patients ($p=0.009$); between anxiety and flares in CD and UC ($p=0.070$ and $p=0.044$, respectively) and between depression and flares in UC ($p=0.013$); depression and surgery in CD ($p=0.007$); anxiety and biologics use and depression and biologics use in CD ($p<0.001$ and $p=0.016$, respectively); depression and steroids use in CD ($p=0.035$) and anxiety and steroids use in UC ($p=0.013$).

DISCUSSION

This study is the largest to date prospective design on the relationship between depression and anxiety and clinical recurrence in IBD. While previous prospective studies on the topic exist, due to small samples, short observation periods and inconsistencies in measuring depression/anxiety and disease activity, the relationship between depression, anxiety and disease activity in IBD has been controversial.

Examining the longitudinal data of over 2,000 Swiss IBD participants, we found that symptoms of depression are associated with clinical recurrence, with those depressed having a significantly shorter time to a clinical recurrence event. The link between depressive symptoms and clinical recurrence appears stronger in participants with CD, which has been previously reported in several much smaller studies.(12) Our study's results are consistent with the results of seven out of 12 previous prospective studies,(8, 16, 19-21, 23, 24) offering, however, a significantly larger sample and the observations conducted from 2006 till 2015, and thus the longest to date. In addition, our approach to defining clinical recurrence was different than in the previous studies as we used a composite outcome measure while the majority of studies relied solely on a single disease activity measure such as the Crohn's Disease Activity Index (CDAI) which can be highly subjective. Opting to rely on physician-reported flare events, fistulas and stenosis (for CD only), IBD surgery, and steroids or biologics intake has allowed us to provide a more robust and likely less biased measure of clinical recurrence than relying on a single disease activity measure.

While anxiety is a more prevalent mental disorder than depression [its 12-month prevalence in IBD is 17.9% as compared to 10.5% for mood disorders(31)], the role played by anxiety in terms of its negative influence on IBD activity seems less pronounced than that of depression.

Anxiety frequently coexists with depression and together with psychological stress, which is best examined of the three in the context of IBD, they impact inflammation.(32) Stress has also been linked to disease activity in 13 out of 18 prospective studies systematically reviewed by Camara et al.(33) Nevertheless, as there is a lack of research differentiating between depression and anxiety in terms of their specific impact on inflammation in IBD, it is unknown whether pathophysiology of either disorder can explain a stronger relationship of depression to clinical recurrence in IBD in the present study. It is, however, clear that symptoms of depression such as, for example, loss of interest in daily activities may lead to non-compliance with IBD treatment,(11) which, in turn, can lead to a flare. In addition, anxiety is often not a constant symptom in IBD participants but rather related to a situation, for example, it can rise when patients have no easy access to a toilet but then drops to a normal level when the patient returns home. It is thus possible that an ongoing character of depressive symptoms is responsible for its strong relationship with clinical recurrence.

Finally, this study unavoidably has limitations. One of them is reliance on patient self-report in psychological measures. A psychological diagnostic interview would likely provide more accurate rates of depression and anxiety than the HADS which is a screening measure unable to provide a diagnosis. Further, there is an ongoing controversy on the usefulness of the HADS. Some studies show it to be equally good in detecting anxiety and depression as the widely used Brief-PHQ(34) and better than another widely used scale the General Health Questionnaire (GHQ)(34, 35). The 2002 update to a literature review on the HADS validity, including 747 research papers, concluded that it performs well in assessing symptom severity and caseness of anxiety and depression in somatic, psychiatric and primary care patients, and in the general population.(36) On the other hand, the recent psychometric systematic reviews showed the HADS to be a measure of a state of general psychological distress rather than

unique mood states.(37, 38) Other measures may potentially more accurately report on these symptoms, however, it is, as yet, unclear, which questionnaire is best for depression and anxiety screening in IBD. To date, it is the HADS that has been used most commonly in the studies on IBD (39) and thus it is the scale that facilitates comparisons with previous studies. In any case, the controversy around the HADS's performance had been unknown at the time the cohort was set up. Another limitation are annual intervals between each follow-up, which, while practical in the study of this size, may lead to underreporting of clinical recurrence events. In addition, patients themselves may underreport disease events to doctors, leading to further underreporting of disease activity. The cohort, while large, is not population-based and thus the study results may not be necessarily generalizable to the whole IBD population.

CONCLUSION

Depression (and to some degree anxiety as well) is strongly associated with clinical recurrence over time. It thus seems prudent to recommend that screening for common mental disorders and referring for psychological/psychiatric treatment should be included in standard IBD care. Whether this improves patient outcomes and is cost-effective remains to be established. Studies in other populations do not always support the value of routine screening particularly in primary care,(40) though populations with chronic conditions or with a history of depression or other mental health problems may benefit from such screening.(41) As occurrence of depression appears to shorten the time to a clinical recurrence event, resulting in flares and complications, and thus, consequently, a more aggressive treatment, prevention and early detection of depression could potentially reduce not only individual patient's suffering, but also healthcare costs. Stepped care or collaborative care models might facilitate this,(42) and their efficacy has been investigated in the context of IBD, with encouraging results.(43-45)

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Table 1: Characteristics of the sample at baseline

	CD	UC or IC	Total
Total Number of Patients	1122 (55.9)	885 (44.1)	2007
(%)			
Age (in years)			
Median, q25 – q75,	40.2, 28.5 – 52.6,	41.0, 30.9 – 52.1,	40.5, 29.7 – 52.4,
min – max	15.8 – 87.5	16.5 – 82.8	15.8 – 87.5
Males (%)	512 (45.6)	458 (51.8)	970 (48.3)
Disease duration (in years)			
Median, q25 – q75,	8.17, 2.5 – 17.2,	6.2, 2.0 – 13.4,	7.2, 2.2 – 15.5,
min – max	0.03 – 52.5	0.03 – 46.2	0.03 – 52.5
CD location at baseline			
L1 (ileal)	252 (22.5)		
L2 (colonic)	245 (21.8)		
L3 (ileo-colonic)	516 (46.0)		
L4 (Upper GI only)	9 (0.8)		
<i>Unclear/Unknown</i>	<i>100 (8.9)</i>		
UC/IC location at baseline			
Proctitis		329 (37.2)	
Left-sided colitis		293 (33.1)	
Pancolitis		170 (19.2)	
<i>Unclear/Unknown</i>		<i>93 (10.5)</i>	
CDAI at baseline			
Median, q25 – q75,	36.5, 14 – 81,		

min – max	0 – 450		
MTWAI at baseline			
Median, q25 – q75, min – max		3, 1 – 5, 0 – 19	
Anxiety symptoms at baseline			
None	679 (60.5)	576 (65.1)	1255 (62.5)
Mild	241 (21.5)	183 (20.7)	424 (21.1)
Moderate	157 (14.0)	98 (11.1)	255 (12.7)
Severe	45 (4.0)	28 (3.2)	73 (3.6)
Depression symptoms at baseline			
None	881 (78.5)	721 (81.5)	1602 (79.8)
Mild	142 (12.7)	111 (12.5)	253 (12.6)
Moderate	78 (7.0)	40 (4.5)	118 (5.9)
Severe	21 (1.9)	13 (1.5)	34 (1.7)

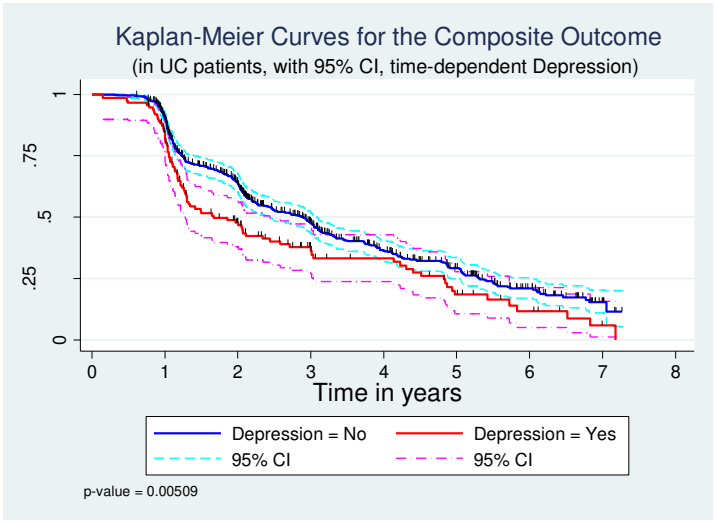
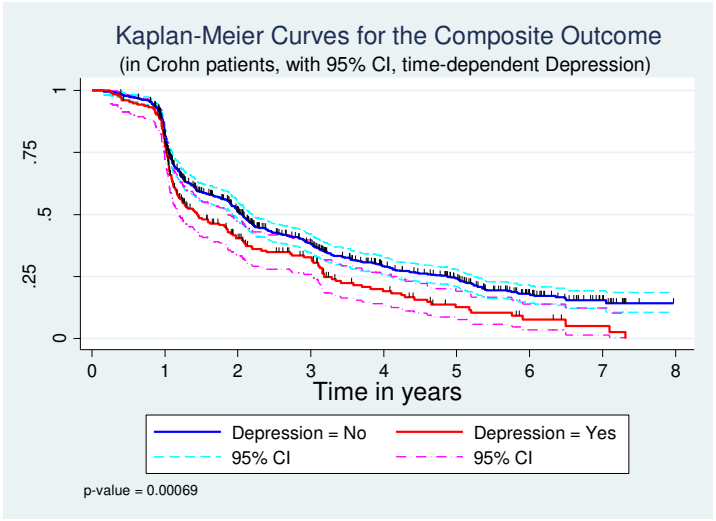
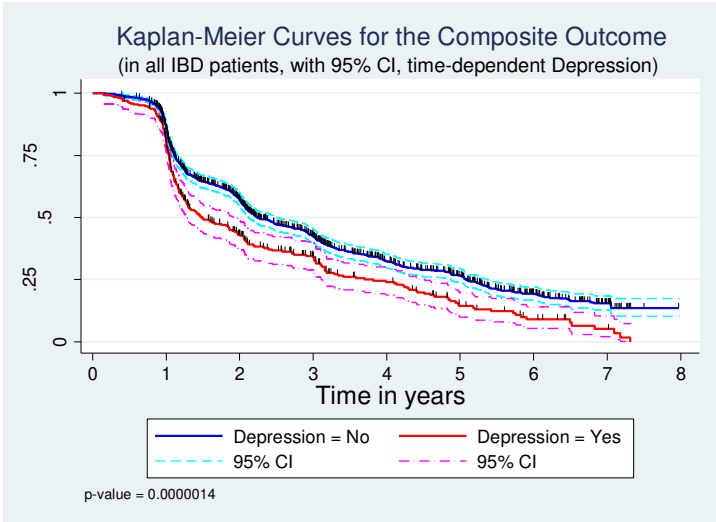


Figure 1: Depression symptoms and disease activity over time

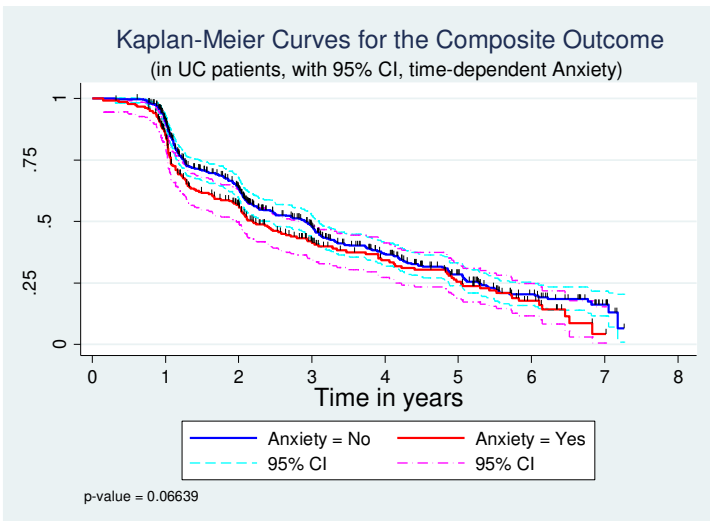
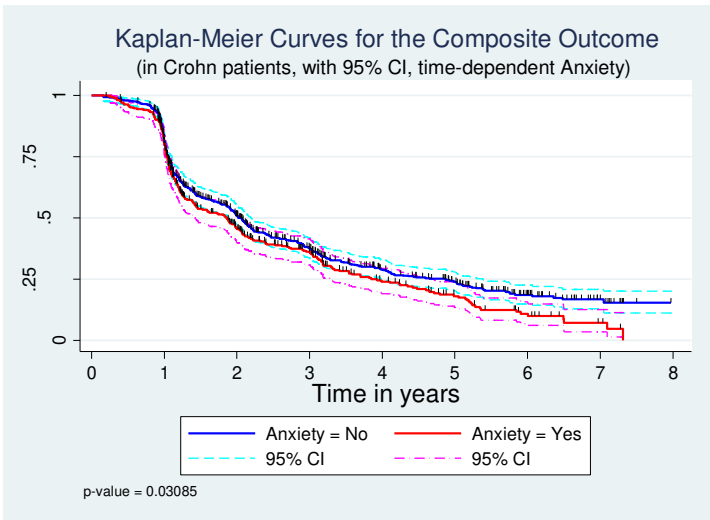
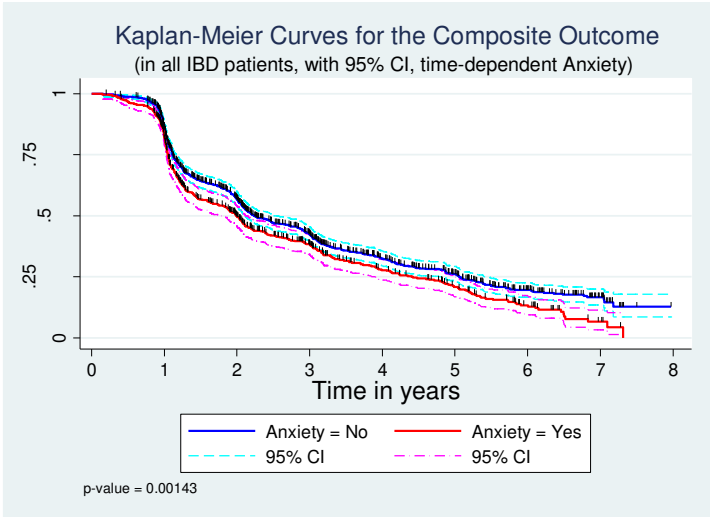


Figure 2: Anxiety symptoms and disease activity over time