Temporal Comorbidity of Mental Disorder and Ulcerative Colitis

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ABSTRACT

Objectives: Ulcerative colitis is an inflammatory bowel disease that rarely exists in isolation in affected patients. We examined the association of ulcerative colitis and International Classification of Diseases mental disorder, as well as the temporal comorbidity of three broad International Classification of Diseases groupings of mental disorders in patients with ulcerative colitis to determine if mental disorder is more likely to occur before or after ulcerative colitis.

Methods: We used physician diagnoses from the regional health zone of Calgary, Alberta, for patient visits from fiscal years 1994 to 2009 for treatment of any presenting concern in that Calgary health zone (763,449 patients) to identify 5113 patients age younger than 1 year to age 92 years (2120 males, average age = 47 years; 2993 females, average age = 48 years) with a diagnosis of ulcerative colitis.

Results: The 16-year cumulative prevalence of ulcerative colitis was 0.0058%, or 58 cases per 10,000 persons (95% confidence interval = 56-60 per 10,000). Although the cumulative prevalence of mental disorder in the overall sample was 5390 per 10,000 (53.9%), we found that 4192 patients with ulcerative colitis (82%) also had a diagnosis of a mental disorder. By annual rate of ulcerative colitis, patients with mental disorder had a significantly higher annual prevalence. The mental disorder grouping neuroses/depressive disorders was most likely to arise before ulcerative colitis (odds ratio = 1.87 for males; 2.24 for females).

Conclusions: A temporal association was observed between specific groups of International Classification of Diseases mental disorder and ulcerative colitis, indicating a possible etiologic relationship between the disorders or their treatments, or both.

INTRODUCTION

Ulcerative colitis is a form of inflammatory bowel disease (IBD) characterized by inflammation of the colonic mucosa.[1] Inflammation typically begins in the rectum and spreads proximally through the colon in a continuous manner. The hallmark clinical features of ulcerative colitis are recurrent flares associated with painful, bloody diarrhea followed by spontaneous remission. During acute flares, severe inflammation can lead to major complications, such as blood loss and toxic megacolon.

The pathogenesis of ulcerative colitis is poorly understood and represents a complex interaction between heredity, immune dysregulation, and environment. Ulcerative colitis is a disease with an annual incidence ranging from 6.3 to 24.3 per 100,000 person-years that is higher in industrialized nations.[2] A Western lifestyle and environment appear to be risk factors for ulcerative colitis because of its emergence in nations undergoing industrialization.[2]

Diagnosis, prognostication, and treatment planning necessitate endoscopic and histologic studies. The degree of inflammation and extent of disease guide therapy, which is to first induce remission and then maintain remission.[1] Whereas the treatment paradigms for ulcerative colitis have substantially changed with the advent of biologic therapy, subgroups of affected patients fail to respond or lose treatment response, presenting challenges in disease management. A recent review identifies a range of clinical factors to consider as an empirical rationale for modifying treatment.[3] Factors determining the variability in response to treatment are likely manifold, including individual differences in genetics, environment, and immune dysregulation. Moreover, as ulcerative colitis is a chronic disease with long survival rates, the potential cannot be ignored for comorbidities to interact with and to complicate the ulcerative colitis vulnerability, disease processes, and treatment.

Román and Muñoz[4] reviewed the comorbidities associated with IBD, including mental disorder. The authors pointed out that affective disorders have been extensively studied in patients with IBD, whereas data on conditions such as psychoses and other mental disorders are scarce. Recently, a standard systematic review protocol was established to investigate the putative linkage between IBD and psychological factors, which, although suspected, has not been established.[5] This protocol was developed largely as a response to previous reviews concerned with this link that had conceptual and methodologic limitations. Although the proposed protocol is comprehensive, it has not yet been implemented, in part because of the extensive reliance on the assimilation of high-quality research.[5] In the meantime, informatics approaches may provide additional insights relevant to the understanding of the relationship of not just psychological factors but also other somatic and biologic factors of ulcerative colitis.

In this study, we focused on the diagnosis of ulcerative colitis, recognizing that it rarely exists in isolation but is rather part of a complex matrix of disorders arising in patients over time. We examined three main groupings of mental disorder, composed of specific ranges of mental disorder codes in the International Classification of Diseases (ICD),

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to illustrate the temporal relationship with ulcerative colitis on the basis of the index (first occurrence) diagnosis of mental disorder and ulcerative colitis. This article is the first, to our knowledge, to describe the prevalence and temporal comorbidity of mental disorder and ulcerative colitis as it arises in affected individuals in a population. The examined relationship between ulcerative colitis and mental disorder in a regional population in Canada provides additional insight into the etiology of ulcerative colitis.

METHODS

With use of a population-based sampling frame, 763,449 patients (45.8% male) were selected from the regional health service registry (Calgary, Alberta, Canada) and merged with all direct physician billings from 1993 to 2010 for treatment of any presenting concern. Each billing record pertains to services rendered to patients on specified dates resulting in assignment of an ICD (Version 9) diagnostic code. This study employed anonymous data that included ICD diagnoses, visit date, age at index visit, and sex.

The overall cumulative 16-year prevalence and the annual prevalence rates were, respectively, based on the number of unique patients in whom a physician diagnosed ulcerative colitis in the overall 16-year sample and in any given year, denominated by the civic census from 1994 to 2009. These years represent the interval having full fiscal years for which data were available. Unique implies that each patient was counted only once in a given period. Preliminary analysis indicated male-female differences in rates; hence, further analyses included stratification on the basis of sex to control for this effect.

The data were collapsed into 2 basic groups representing the presence or absence of ulcerative colitis. All psychiatric diagnoses (ICD Codes 290-319) were collapsed into 3 general groupings on the basis of the presence or absence of specific ranges of the following mental disorders: psychotic disorders (Codes 290-299, not including major depression); neuroses/depressive disorders, a group including anxiety

disorders; as well as major depression and depressive disorders (ie, Codes 296.2, 296.3, 300, 308, 309, 311); and a group consisting of all other mental disorders (all remaining ICD mental disorder codes). The data were stratified further on the basis of the temporal occurrence of the index diagnoses of either mental disorder or ulcerative colitis. The 3 cases in which both diagnoses were assigned on the same day were assigned to the group "mental disorder after ulcerative colitis."

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated on the basis of individual counts in each cell using the stratifications noted earlier. Criteria related to group classification of the data were developed to ensure that the 3 psychiatric groupings were independent.

Analyses of rates and ORs were based on comparison of overlapping and nonoverlapping 95% CIs. For rates, significant statistical differences between proportions in any given year were estimated by comparison of the 95% CIs using the standard formula, wherein nonoverlapping 95% CIs represent significant differences ($p < 0.05$, with Z set to 1.96) and overlapping 95% CIs indicate statistical nonsignificance.

On the basis of the index (first) diagnosis date among those with ulcerative colitis and three groupings of mental disorder, two time-based groups were identified regarding whether mental disorder arose before or after ulcerative colitis. The main comparisons within groups of mental disorder and ulcerative colitis were based on the temporal order of each of the three mental disorder groupings being associated with ulcerative colitis, as represented by ORs. The ORs were independent of the temporal order and examined only the likelihood in independent mental disorder groups of arising either before or after ulcerative colitis. Therefore, the hypothesis was constructed on the assumption that the respective ORs in mental disorder groups, arising either before or after ulcerative colitis, would be significantly different from one another. Between-mental disorder group comparisons provided an indication of mental disorder group similarity or differences in magnitude and direction of the relationship.

RESULTS

In the dataset there were 5113 patients ranging in age from younger than 1 year to 92 years old (2120 males, mean

Table 1. Ulcerative colitis regional population rates (per 10,000) by sex with or without mental disorder, 1994-2009				
	Males (95% CI)		Females (95% CI)		
Year	No mental disorder	Mental disorder	No mental disorder	Mental disorder	Total rate[a] (95% CI)
1994	6 (5-7)	28 (26-30)	6 (5-7)	50 (48-52)	39 (37-41)
1995	7 (6-8)	30 (28-32)	5 (4-6)	52 (50-54)	42 (40-44)
1996	7 (6-8)	30 (28-32)	5 (4-6)	51 (49-53)	40 (38-42)
1997	6 (5-7)	30 (28-32)	6 (5-7)	50 (48-52)	40 (39-41)
1998	7 (6-8)	29 (27-31)	5 (4-6)	50 (48-52)	40 (39-41)
1999	6 (5-7)	29 (27-31)	6 (5-7)	49 (47-51)	39 (38-40)
2000	6 (5-7)	28 (26-30)	5 (4-6)	48 (46-50)	38 (37-39)
2001	6 (5-7)	28 (26-30)	6 (5-7)	48 (46-50)	38 (37-39)
2002	6 (5-7)	28 (26-30)	6 (5-7)	46 (44-48)	37 (36-38)
2003	6 (5-7)	26 (25-27)	6 (5-7)	43 (41-45)	35 (34-36)
2004	6 (5-7)	27 (26-28)	6 (5-7)	45 (43-47)	36 (35-37)
2005	6 (5-7)	27 (26-28)	6 (5-7)	45 (43-47)	36 (35-37)
2006	6 (5-7)	26 (25-27)	6 (5-7)	43 (41-45)	34 (33-35)
2007	6 (5-7)	24 (23-25)	6 (5-7)	41 (39-43)	33 (32-34)
2008	6 (5-7)	23 (22-24)	6 (5-7)	39 (37-41)	31 (30-32)
2009	6 (5-7)	22 (21-23)	5 (4-6)	37 (35-39)	30 (29-31)

[a] Males and females combined with and without mental disorder.
CI = confidence interval.

age = 47 years; 2993 females, mean age = 48 years), each of whom received a diagnosis of ulcerative colitis between fiscal years 1994 and 2009. The mean duration of diagnosis from the index date of diagnosis was 759 days (standard deviation [SD] = 1365 days) or 2.1 years (SD = 3.7 years) for females, and for males the average was 853 days (SD = 1443 days) or 2.3 years (SD = 4.0 years).

To determine the burden of ulcerative colitis in our health zone, we calculated its prevalence. The prevalence of ulcerative colitis, although constant in those without mental disorder, decreased in the population with mental disorder during the study period (Table 1).

The cumulative prevalence of mental disorder in the Calgary health zone has been described.[6] Mental disorder was present in 53.9% of patients from the overall sample (n = 763,449). In the sample of those with a diagnosis of ulcerative colitis, 4192 (82%) had a mental disorder. Consistent with the proportions observed in the larger group, the ulcerative colitis group was 58% female. A diagnosis of mental disorder preceded a diagnosis of ulcerative colitis by an average of 1713 days (SD = 1294 days) or 4.7 years (SD = 3.5 years). A diagnosis of ulcerative colitis preceded a diagnosis of mental disorder, on average, by 1386 days (SD = 1141 days) or 3.8 years (SD = 3.1 years).

The 16-year cumulative prevalence rate for ulcerative colitis was 58 per 10,000 (95% CI = 56-60). Table 1 shows the annual population rates in the health region for ulcerative colitis for males and females with and without mental disorder. Comparison of the CIs indicates that for both sexes having any mental disorder significantly increases the rate of ulcerative colitis in each year. Furthermore, although there was no apparent difference in the CIs of either sex without a mental disorder, female rates by year were significantly higher than those observed for males.

In the groups with no mental disorder, the rates of ulcerative colitis remained stable, whereas those for males and females having any mental disorder peaked in 1996 and significantly decreased in subsequent years, as demonstrated by a comparison of nonoverlapping CIs.

Table 2 presents the data on which the ORs and CIs in Table 3 were calculated. The groups representing mental disorder occurring in time before or after ulcerative colitis are independent within each strata (eg, psychotic disorders; neuroses/depressive disorders; and other disorders, which included all other ICD diagnoses). For each grouping of mental disorder, the OR compared the presence or absence of mental disorder given the presence or absence of ulcerative colitis.

In Table 3, comparison of the CIs of the ORs indicated that unlike psychotic disorders, neuroses/depressive disorders as a group of mental disorders were significantly more likely to occur before ulcerative colitis for both males and females. Other mental disorders as a group were significantly more likely to arise before ulcerative colitis for females. However, for males, only other mental disorders were significantly less likely to arise after ulcerative colitis. Neuroses/depressive disorders were most likely to arise before ulcerative colitis for both sexes.

DISCUSSION

Ulcerative colitis is an inflammatory disease of the rectum and colon causing substantial morbidity. Although the exact etiology of ulcerative colitis remains unknown, a combination of genetic predisposition and environmental risk factors underlie its pathogenesis.[7] Unlike the findings from our study, Molodecky et al[2] found that ulcerative colitis appears to be on the rise around the globe. Ulcerative colitis is more prevalent in developed nations, with the highest prevalence in Europe (51 per 10,000 persons) and North America (25 per 10,000 persons).[2]

Consistent with these data, the annual overall prevalence of ulcerative colitis, inferred from physician diagnosis, in the Calgary health zone was highest in 1996 (40 per 10,000) and steadily decreased to 30 per 10,000 in 2009. Whereas the annual prevalence was the same for males and females among those without any mental disorder, with a maximum of 7 per 10,000, the annual prevalence was much higher for those with any mental disorder, with males

Table 2. Count of patients by sex in each diagnostic grouping by mental disorder and ulcerative colitis						
Sex	Temporal order of mental disorder	Mental disorder group	No ulcerative colitis, no mental disorder	Ulcerative colitis, no mental disorder	No ulcerative colitis, mental disorder	Ulcerative colitis, mental disorder
Female	Before ulcerative colitis	Psychotic disorders	369,555	2432	41,755	262
		Other disorders	293,728	1645	117,582	864
		Neuroses/depression	167,486	547	243,824	1787
	After ulcerative colitis	Psychotic disorders	369,555	2432	41,755	299
		Other disorders	293,728	1645	117,582	484
		Neuroses/depression	167,486	547	243,824	659
Male	Before ulcerative colitis	Psychotic disorders	316,586	1798	30,440	142
		Other disorders	242,660	1201	104,366	548
		Neuroses/depression	203,633	695	143,393	917
	After ulcerative colitis	Psychotic disorders	316,586	1798	30,440	180
		Other disorders	242,660	1201	104,366	371
		Neuroses/depression	203,633	695	143,393	508

and females having maximum annual prevalence rates of 30 per 10,000 and 52 per 10,000, respectively. The 16-year cumulative prevalence in the population was 58 per 10,000, which is in keeping with the rates observed in Europe. Even though the overall rates are comparable, the reduction observed in the annual prevalence over time in ulcerative colitis for those with mental disorder and the constant rate in those with no mental disorder was opposite to the increases reported in the literature. As with the range of rates reported in the literature, differences in the methods, data sources, and diagnostic precision may account for different findings.

We found that a significant portion of patients with ulcerative colitis also had mental disorder. Preliminary evidence indicates a link between inflammation and a subset of mental disorder, namely mood disorders.[8] A recent study quantified this association by showing that hospitalization for infection and autoimmune disease increased the risk of a mood disorder developing by 62% and 45%, respectively.[8] In this study, there were distinct patterns of mental disorder that preceded and followed ulcerative colitis, principally the ICD group consisting of neuroses and depressive disorders. This study most closely resembles that of Kurina et al,[9] who examined the temporal relationship of depression in patients with IBD. Groups were also distinguished in terms of depression arising

either before or after bowel disorder, being either etiologic or consequential. The present study extends these results in terms of describing the broad yet temporally distinct groups of mental disorder diagnosed in association with ulcerative colitis in a population.

Presently, there is no satisfactory explanation for the observed patterns of mental disorder and ulcerative colitis. Future research is required to examine this observation in more detail. One possibility is the effect on inflammation and the autoimmune response of psychotropic medications used to treat anxiety and depression, a mechanism that may play a role in the etiology of ulcerative colitis and a hitherto unexamined, long-term risk of long-term medication use. We hope to examine this relationship specifically in relation to anxiety, autoimmune disorders, and ulcerative colitis.

It is not surprising to find that certain mental disorders occur either before or after ulcerative colitis, given that ulcerative colitis has a peak incidence between the second and fourth decades of life.[2] Disorders such as those specifically diagnosed in early childhood would naturally arise before ulcerative colitis. Likewise, a mental disorder such as dementia associated with functional decline later in life would naturally be expected to occur, on average, after a diagnosis of ulcerative colitis. Further analysis on the basis of inclusion and

exclusion of age-related disorder stratifications is warranted. The explanation for the observed temporal relationship between mental disorder and ulcerative colitis based on confounding by age, in which the natural histories of the various disorders manifest themselves at different ages, is feasible. However, the presence of distinct patterns of specific groups of disorders arising before or after ulcerative colitis may also point to a common underlying genetic vulnerability. Moreover, if random processes underpinned the observed temporal profiles of mental disorders arising either before or after ulcerative colitis, one would not expect such substantial differences in the time between onset of specific mental disorder preceding or following ulcerative colitis. More detailed examination of the temporal precedence of mental disorders in those with ulcerative colitis is indicated given the overrepresentation of mental disorder in the ulcerative colitis group (81%) compared with the general population (53.9%).

Limitations

The diagnostic groupings combined diagnoses into two relatively coherent ICD diagnostic groupings (psychotic disorders and neuroses/depressive disorders) on the basis of more common pharmacologic treatments, as well as one more heterogenous catchall grouping (other). Although the groupings provided a "broad-stroke" approach to examination of the relationship between ulcerative colitis and mental disorder, given the overrepresentation of mental disorder among those with ulcerative colitis, more specific diagnosis-related associations may well be masked. For example, that psychoses were found not to have any temporal relationship with ulcerative colitis does not mean that there are not psychotic disorders that, when studied individually, may be discovered to have similar effects. Ultimately, a detailed analysis of all diagnoses is warranted.

Another study limitation is the precision (reliability and validity) of physician diagnosis. Lack of precision affects all research that is based on diagnosis at some level in terms of false-positive

Table 3. Odds ratios of mental disorder groups given before and after ulcerative colitis by sex and temporal occurrence of ulcerative colitis

Sex	Temporal order of mental disorder	Mental disorder group	Odds ratio (95% CI)
Female	Before ulcerative colitis	Psychotic disorders	0.95 (0.84-1.08)
		Other disorders[a]	1.31 (1.21-1.43)
		Neuroses/depression[a]	2.24 (2.04-2.47)
	After ulcerative colitis	Psychotic disorders	1.09 (0.96-1.23)
		Other disorders[a]	0.73 (0.66-0.81)
		Neuroses/depression[a]	0.83 (0.74-0.93)
Male	Before ulcerative colitis	Psychotic disorders	0.82 (0.69-0.97)
		Other disorders	1.06 (0.96-1.17)
		Neuroses/depression[a]	1.87 (1.7-2.07)
	After ulcerative colitis	Psychotic disorders	1.04 (0.89-1.21)
		Other disorders[a]	0.72 (0.64-0.81)
		Neuroses/depression	1.04 (0.93-1.16)

[a] p < 0.05
CI = confidence interval.

and false-negative rates of diagnosis. One could assume that each category or diagnosis suffers more or less equally from this problem to the extent that one could expect a random distribution of more or less accurate diagnoses based on physician expertise.

Finally, for simplicity, only the specific ICD diagnosis of ulcerative colitis was considered in this study. Other related bowel diseases, such as Crohn disease, were not included in the grouping. The relationship between a wider grouping of bowel diseases and the mental disorder groupings remains unknown. Also unknown is the degree to which ulcerative colitis or mental disorder is overrepresented in other disorders or whether other disorders are overrepresented in ulcerative colitis more than mental disorder.

Future Directions

The present study examined the relation of three broad groups of mental disorder and ulcerative colitis in the temporal order of the mental disorder group occurring before or after ulcerative colitis. Although neurotic and depressive disorders were shown to have a statistically and epidemiologically significant temporal relationship with the onset of ulcerative colitis, the disorders accounting for this effect were not identified specifically. As such, the present study points to a novel direction, which will guide further research and education, rather than a conclusive exposition of clinical fact that may be translated into practice.

Understanding of ulcerative colitis is well developed in current clinical and diagnostic knowledge, with new treatment options for this condition having been identified.[10] However, there has been little description of the profile of disorders associated with ulcerative colitis. The present article describes the relationship of specified mental disorder groups that arise in temporal association with ulcerative colitis. Of note is that mental disorder represents 1 main class of ICD disorders among 18 main ICD classes in total.

The challenge to future research lies in the difficulty of representing the spatial and temporal complexity of how disorders emerge in patients across time. Additionally, ulcerative colitis is one dependent variable in a collection of disorders related to a much broader class of disorders affecting not only the bowel but the entire digestive system. Yet, the approach to understanding the etiologic and prognostic effect of comorbidity on ulcerative colitis tends to focus on individual disorders or small clusters of similar disorders. Common symptoms underpin our understanding of ulcerative colitis and related diseases in addition to our evolving understanding of the biochemical and genetic substrates and mechanisms giving rise to disease. It is apparent from the present study that there is useful information embedded in the diagnostic profiles of clinical populations.

The present example of population-based diagnostic analysis represents a novel approach to organize thinking about the relationship between diagnostic classifications for how patterns of diagnosis emerge in populations over time. Information emerging from this approach challenges traditional thinking about disease processes and may actually influence the organization of health services designed to treat specific disorders in clinical pathways. The present research is in some ways similar to the recently identified epistemologic threat to the validity of medical knowledge that is based on how medical research is designed and implemented.[11] The profile of mental disorder associated with ulcerative colitis represents a complex yet virtually unexamined source of influence on treatment effect. Studies are most often limited to the examination of one or two associated clinical conditions. Using the present dataset, we have the opportunity to coherently examine and rank the associations in time of ulcerative colitis and all disorders.

Evidence suggests that serotonin reuptake inhibitors may play a role in immune dysregulation.[12-14] Although this evidence has not been explicitly studied in relationship to the etiology of ulcerative colitis, the present findings suggest that there may be a link, given that most anxiety and depressive disorders have been treated with oral serotonin reuptake inhibitors. Hence, on the basis of the present findings, it is reasonable to postulate that future research may fruitfully focus on this putative link. Serotonin receptors are no doubt ubiquitous throughout the human body and may be involved in regulation of the immune response underpinning ulcerative colitis. This tenuous example serves to illustrate a main finding emerging from this approach to the analysis of diagnostic data. Regarding the etiology of ulcerative colitis, the pharmacologic treatment of mental disorder and the mental disorder itself are confounded in terms of the putative effect on emergence of ulcerative colitis.

Finally, in our past population-based studies using this same dataset, we have provided validation of the adverse childhood experiences study.[6] In those studies the main assumption was that early adversity is one gateway to mental disorder in later life, and we demonstrated a clear relationship between mental disorder and biomedical or somatic disorders. More importantly, additional studies have drawn associations between somatic disorders, specifically ulcerative colitis and early adversity.[15] Use of our current, novel approach to expand analysis of the temporal comorbidity of mental disorder and specific biomedical and somatic disorders may help to extend understanding of the potentially confounding treatment and etiologic factors as these emerge over time in the complex relationship between experience and health status. ❖

References

1. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med 2011 Nov 3;365(18):1713-25. DOI: http://dx.doi.org/10.1056/NEJMra1102942.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012 Jan;142(1):46-54.e42. DOI: http://dx.doi.org/10.1053/j.gastro.2011.10.001.

3. Lorinczy K, Miheller P, Kiss SL, Lakatos PL. [Epidemiology, predictors and clinical aspects of loss of response to biological therapy]. [Article in Hungarian]. Orv Hetil 2012 Feb 5;153(5):163-73. DOI: http://dx.doi.org/10.1556/OH.2012.29294.

4. Román AL, Muñoz F. Comorbidity in inflammatory bowel disease. World J Gastroenterol 2011 Jun 14;17(22):2723-33. DOI: http://dx.doi.org/10.3748/wjg.v17.i22.2723.

5. Schoultz M, Atherton I, Hubbard G, Watson AJ. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a protocol for systematic review of prospective cohort studies. Syst Rev 2013 Jan 23;2:8. DOI: http://dx.doi.org/10.1186/2046-4053-2-8.

6. Cawthorpe D. A novel population-based health index for mental disorder. Perm J 2013 Spring;17(2):50-4. DOI: http://dx.doi.org/10.7812/TPP/12-081.

7. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012 Nov 3;380(9853):1606-19. DOI: http://dx.doi.org/10.1016/S0140-6736(12)60150-0.

8. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry 2013 Aug;70(8):812-20. DOI: http://dx.doi.org/10.1001/jamapsychiatry.2013.1111.

9. Kurina LM, Goldacre MJ, Yeates D, Gill LE. Depression and anxiety in people with inflammatory bowel disease. J Epidemiol Community Health 2001 Oct;55(10):716-20. DOI: http://dx.doi.org/10.1136/jech.55.10.716.

10. Di Sabatino A, Biancheri P, Rovedatti L, Macdonald TT, Corazza GR. Recent advances in understanding ulcerative colitis. Intern Emerg Med 2012 Apr;7(2):103-11. DOI: http://dx.doi.org/10.1007/s11739-011-0719-z.

11. Ioannidis JP. Why most published research findings are false: author's reply to Goodman and Greenland. PLoS Med 2007 Jun;4(6):e215. DOI: http://dx.doi.org/10.1371/journal.pmed.0040215.

12. Fornaro M, Martino M, Battaglia F, Colicchio S, Perugi G. Increase in IL-6 levels among major depressive disorder patients after a 6-week treatment with duloxetine 60 mg/day: a preliminary observation. Neuropsychiatr Dis Treat 2011;7:51-6. DOI: http://dx.doi.org/10.2147/NDT.S16382.

13. Roman A, Vetulani J, Nalepa I. Effect of combined treatment with paroxetine and transcranial magnetic stimulation (TMS) on the mitogen-induced proliferative response of rat lymphocytes. Pol J Pharmacol 2002 Nov-Dec;54(6):633-9.

14. Lin A, Song C, Kenis G, et al. The in vitro immunosuppressive effects of moclobemide in healthy volunteers. J Affect Disord 2000 Apr;58(1):69-74. DOI: http://dx.doi.org/10.1016/S0165-0327(99)00076-2.

15. Masuda A, Yamanaka T, Hirakawa T, et al. Intra- and extra-familial adverse childhood experiences and a history of childhood psychosomatic disorders among Japanese university students. Biopsychosoc Med 2007 Apr 2;1:9. DOI: http://dx.doi.org/10.1186/1751-0759-1-9.

Disease

We are accustomed to speak of "disease entities" as though they had an independent, individual existence and could be recognized as friends—or better, perhaps, as enemies. This is … one of those abstractions that do violence to the reality of the … situation, for there is no disease aside from the patient. The disease is the change produced in the patient by the pathological process. Diagnosis involves the observation of the patient as he is, and … a reconstruction in imagination of the patient as he was, before afflicted. The disease is the difference between those two pictures.

— *Glomerular Nephritis,* Thomas Addis, 1881-1949,
English physician-scientist and pioneer in the field of nephrology