Published in final edited form as:
J Psychosom Res. 2013 August ; 75(2): 121–127. doi:10.1016/j.jpsychores.2013.04.007.

Associations between DSM-IV mental disorders and onset of self-reported peptic ulcer in the World Mental Health Surveys

Kate M. Scott, PhD[1], **Jordi Alonso, MD, PhD**, **Peter de Jonge, PhD**, **Maria Carmen Viana, MD, PhD**, **Zhaorui Liu, MD, MPH**, **Siobhan O'Neill, PhD**, **Sergio Aguilar-Gaxiola, MD, PhD**, **Ronny Bruffaerts, PhD**, **Jose Miguel Caldas-de-Almeida, MD, PhD**, **Dan J. Stein, MD, PhD**, **Matthias Angermeyer, MD**, **Corina Benjet, PhD**, **Giovanni de Girolamo, MD**, **Ingrid-Laura Firuleasa, MD, MSc**, **Chiyi Hu, MD, PhD**, **Andrzej Kiejna, MD, PhD**, **Viviane Kovess-Masfety, MD, PhD**, **Daphna Levinson, PhD**, **Yoshibumi Nakane, MD**, **Marina Piazza, MPH, ScD**, **José A. Posada-Villa, MD, MS**, **Mohammad Salih Khalaf, MD**, **Carmen C. W. Lim, MSc**, and **Ronald C. Kessler, PhD**

Abstract

Objective—Recent research demonstrating concurrent associations between mental disorders and peptic ulcers has renewed interest in links between psychological factors and ulcers. However, little is known about associations between temporally prior mental disorders and subsequent ulcer onset. Nor has the potentially confounding role of childhood adversities been explored. The objective of this study was to examine associations between a wide range of temporally prior DSM-IV mental disorders and subsequent onset of ulcer, without and with adjustment for mental disorder comorbidity and childhood adversities.

Methods—Face-to-face household surveys conducted in 19 countries (n=52,095; person years=2,096,486).The Composite International Diagnostic Interview retrospectively assessed lifetime prevalence and age at onset of 16 DSM-IV mental disorders. Peptic ulcer onset was assessed in the same interview by self-report of physician's diagnosis and year of diagnosis. Survival analyses estimated associations between first onset of mental disorders and subsequent ulcer onset.

Results—After comorbidity and sociodemographic adjustment, depression, social phobia, specific phobia, post-traumatic stress disorder, intermittent explosive disorder, alcohol and drug abuse disorders were significantly associated with ulcer onset (ORs 1.3-1.6). Increasing number of lifetime mental disorders was associated with ulcer onset in a dose-response fashion. These associations were only slightly attenuated by adjustment for childhood adversities.

[1]Correspondence to: Kate M. Scott, PhD, Department of Psychological Medicine, Otago University, PO Box 913, Dunedin, New Zealand (kate.scott@otago.ac.nz); 64 3 4747007 ext 7369 (voice); 64 3 4747934 (fax).

Competing Interests Statement: Dr. Stein has received research grants and/or consultancy honoraria and/or served on speaker bureaus for Biocodex, Eli-Lilly, GlaxoSmithKline, Lundbeck, Pfizer, Servier, Solvay, and Wyeth. Dr. Kessler has been a consultant for Analysis Group, GlaxoSmithKline Inc., Kaiser Permanente, Merck & Co, Inc., Ortho-McNeil Janssen Scientific Affairs, Pfizer Inc., Sanofi-Aventis Groupe, Shire US Inc., SRA International, Inc., Takeda Global Research & Development, Transcept Pharmaceuticals Inc., Wellness and Prevention, Inc., and Wyeth-Ayerst; has served on advisory boards for Eli Lilly & Company, Mindsite, and Wyeth-Ayerst; and has had research support for his epidemiological studies from Analysis Group Inc., Bristol-Myers Squibb, Eli Lilly & Company, EPI-Q, Ortho-McNeil Janssen Scientific Affairs., Pfizer Inc., Sanofi-Aventis Groupe, and Shire US, Inc. He owns stock in Datastat, Inc.
All other authors have no competing interests to declare.

Conclusions—A wide range of mental disorders were linked with the self-report of subsequent peptic ulcer onset. These associations require confirmation in prospective designs, but are suggestive of a role for mental disorders in contributing to ulcer vulnerability, possibly through abnormalities in the physiological stress response associated with mental disorders.

Keywords

mental disorders; depression; anxiety; alcohol abuse and dependence; peptic ulcer

INTRODUCTION

Earlier research suggested that stress was a causal factor in gastrointestinal ulcer development [1, 2], but the subsequent discovery of the causal role of the *Helicobacter pylori* bacterium sharply diminished interest in stress-related ulcer research[1, 3, 4]. Although further research has established that H-pylori is neither a sufficient nor necessary cause of peptic ulcer [2, 3, 5], interest in stress and other psychological factors in ulcer development has not recovered [6]. Levenstein [6] makes a strong case that this lack of ongoing research into psychological influences in peptic ulcer disease has precluded a more nuanced view of peptic ulcer as a biopsychosocial disease with a complex multifactorial etiology.

In the past decade Goodwin and colleagues have documented concurrent associations between mood and anxiety disorders and self-reported peptic ulcers using large general population samples. [7, 8] These studies have found that associations between several mental disorders and ulcer have persisted after adjustment for mental disorder comorbidity and for comorbid nicotine and alcohol dependence. Other studies with a focus on the health consequences of PTSD have found associations between this disorder and ulcers.[9-11] This body of research focusing on mental disorders provides fresh insight into possible links between psychological factors and peptic ulcer disease. However, two questions arise from these prior studies reporting concurrent associations between mental disorders and peptic ulcers. The first question is the extent to which the mental disorders captured in these associations arose prior to ulcer onset, as would be required by the hypothesis that mental ill-health could contribute to ulcer development. Prospective data that could confirm the temporal sequence of mental disorder-ulcer associations in general population samples appear to be very rare, limited to the Alameda County study which followed 4,595 participants over an 8-10 year period and found that symptom scale measures of depressed mood and hostility were associated with subsequent self-reported peptic ulcer incidence.[12]

The second question arising from the prior studies on concurrent mental disorder-ulcer comorbidity is whether these associations might be confounded by common underlying causes. One such possible confounding factor, or set of factors, is childhood adversities. Childhood physical abuse has now been associated with peptic ulcer in adulthood in several studies.[13-16] It is also well established that childhood abuse and other childhood adversities are strong risk factors for the development of mental disorders in adulthood,[17, 18]. There are three possible models of the joint effects of child abuse and mental disorders. The first is the one just specified whereby child abuse is associated with risk of ulcer onset and mental disorders only appear to be risk factors through their association with child abuse (ie, child abuse is a confounder of associations between mental disorders and ulcer). The second possibility is that child abuse is associated with risk of ulcer onset but that part or all of that association is mediated by mental disorders. The third possibility is that both child abuse and mental disorders could have independent associations with ulcer onset.[19] In this study, because our focus is on mental disorders as possible risk factors, we are testing model 1: whether mental disorders are still associated with ulcers once child abuse is taken into

account. We are not aware of a prior study that has examined associations between mental disorders and peptic ulcers while simultaneously controlling for child abuse and other adversities.

Our aims in the present study were therefore to provide new data on associations between mental disorders and peptic ulcers in a large general population sample with particular attention to these two issues of temporal sequence of associations and control for childhood adversities. This study uses data from the World Health Organization World Mental Health (WMH) Surveys initiative to investigate the associations of a wide range of temporally prior DSM-IV mood, anxiety, impulse control and substance use disorders with subsequent peptic ulcer onset. The WMH surveys retrospectively assessed lifetime history of DSM-IV mental disorders and at the same time obtained self-report of a history of physician's diagnosis of selected physical diseases, including ulcer. The surveys asked respondents to report year of onset of mental disorders and year of ulcer diagnosis; this information enabled the use of survival analysis to examine associations between mental disorders (both type and number) and ulcer onset, restricting the mental disorders examined to those occurring in years prior to the year of ulcer onset. We estimated these associations without and with control for mental disorder comorbidy, sociodemographic variables and smoking history, and a wide range of childhood adversities.

METHOD

Samples and Procedures

This study uses data from 19 of the WMH surveys: Colombia, Mexico, Peru, United States, Shenzhen (China), Japan, New Zealand, Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, Portugal, Israel, Iraq, Northern Ireland, Poland (Table 1). A stratified multi-stage clustered area probability sampling strategy was used to select adult respondents (18 years+) in most WMH countries. All interviews were carried out face-to-face by trained lay interviewers. Most of the surveys were based on nationally representative household samples while Colombia, Mexico and Shenzen were based on nationally representative household (or population register) samples in urbanized areas.

Most surveys used internal subsampling to reduce respondent burden by dividing the interview into two parts. All respondents completed Part 1 which included the core diagnostic assessment of most mental disorders. All Part 1 respondents who met lifetime criteria for any mental disorder and a probability sample of other respondents were administered Part 2 (at the same interview sitting) which assessed physical conditions and collected a range of other information related to survey aims. Part 2 respondents were weighted by the inverse of their probability of selection for Part 2 of the interview to adjust for differential sampling, resulting in an unbiased sample. Analyses in this paper are based on the weighted Part 2 subsample (n=52,095). The weighted (and unweighted) percentages of the Part 2 subsample with lifetime mental disorders are as follows: mood disorders 13.6% (24.7%); anxiety disorders 16.3% (25.7%); impulse control disorders 3.0% (4.9%); substance use disorders 8.2% (10.8%); any mental disorder 28.6% (44.0%). Additional weights were used to adjust for differential probabilities of selection within households, to adjust for non-response, and to match the samples to population sociodemographic distributions. Measures taken to ensure interviewer and data accuracy and cross-national consistency are described in detail elsewhere.[20, 21] All respondents provided written informed consent (see [21] for details).

Measures

Mental disorders—All surveys used the WMH survey version of the WHO Composite International Diagnostic Interview (CIDI 3.0 [20]) to assess lifetime history of mental disorders. Disorders were assessed using the definitions and criteria of *DSM-IV.* The mental disorders included in this paper are: panic disorder, agoraphobia, specific phobia, social phobia, post-traumatic stress disorder, generalized anxiety disorder, obsessive compulsive disorder, major depressive disorder/dysthymia, bipolar broad (I, II and subthreshold), alcohol abuse and dependence, drug abuse and dependence, intermittent explosive disorder, bulimia nervosa and binge eating disorder. CIDI organic exclusion rules were applied in making diagnoses. Clinical reappraisal studies conducted in some of the WMH countries indicate that lifetime diagnoses of anxiety, mood and substance use disorders based on the CIDI have generally good concordance with diagnoses based on blinded clinical interviews. [22]

Ulcer status—In a series of questions adapted from the U.S Health Interview Survey [23], respondents were asked about the lifetime presence of selected chronic conditions. Respondents were asked: “Did a doctor or other health professional ever tell you that you had any of the following illnesses….an ulcer in the stomach or intestine?” If respondents endorsed this question they were classified as having a history of ulcer. Respondents were also asked how old they were when they were first diagnosed with the ulcer. This is referred to as the age of onset of ulcer. For the purposes of this study we refer to this as ‘peptic ulcer’ to differentiate it from other kinds of non-gastrointestinal ulcer, although we acknowledge that it would require access to medical records to confirm that diagnosis.

Childhood adversities—The following childhood adversities were assessed: physical abuse, sexual abuse, neglect, parental death, parent divorce, other parental loss, parental mental disorder, parental substance use, parental criminal behavior, family violence, and family economic adversity. The aim was to assess the occurrence of childhood adversities occurring in the context of the family (not all possible childhood adversities), as these are more likely to be sustained over long periods of time and so to have chronic health effects. Those respondents who reported that the experience occurred before the age of 18 and met the criteria specified for a given adversity were coded as having experienced childhood family adversity. Assessment of the adversities is detailed in prior publications.[24, 25]

Statistical Analysis

Discrete-time survival analyses [26] were used to test sequential associations between first onset of mental disorders and the subsequent onset of ulcer. For these analyses a person-year data set was created in which each year in the life of each respondent up to and including the age of onset of ulcer or their age at interview (whichever came first) was treated as a separate observational record, with the year of ulcer onset coded 1 and earlier years coded 0 on a dichotomous outcome variable. Mental disorder predictors were coded 1 from the year after first onset of each individual mental disorder. This time lag of 1 year ensured that in cases where the first onset of a mental disorder occurred in the same year as ulcer onset, the mental disorder would not count as a predictor. Other independent variables were recorded with the same values from year to year (time invariant predictors such as gender or age at interview) or with dichotomous values that could change from year to year (time-varying predictors). Only person-years up to the onset of ulcer were analyzed so that only mental disorder episodes occurring prior to the onset of ulcer were included in the predictor set. Logistic regression analysis were used to analyze these data with the survival coefficients presented as odds ratios, indicating the relative odds of ulcer onset in a given year for a person with a prior history of a specific mental disorder compared to a person without that

mental disorder (the reference group includes those with no prior history of any mental disorder).

A series of bivariate and multivariate models were developed including the predictor mental disorder plus control variables. Models controlled for person-years, countries, sex, age cohort, and in the multivariate models, other mental disorders. Bivariate models examined association of specific mental disorders with subsequent ulcer onset. The multivariate type model estimated the associations of each mental disorder with ulcer onset adjusting for mental disorder comorbidity (that is, for other mental disorders occurring at any stage prior to the year of ulcer onset). The multivariate number model included a series of predictor variables for number of mental disorders (e.g., one such variable for respondents who experienced exactly one mental disorder, another for respondents who experienced exactly two mental disorders, and so on), as well as the control variables. Other more complex multivariate models were also estimated, for example including both type and number of mental disorders, but model fit statistics best supported the use of the simpler models are reported here (data available on request).

The issue of control for covariates is complex. We prefer to not control for covariates that could be on the causal pathway between mental disorders and subsequent ulcer diagnosis. However, we recognize that these variables may also confound associations. For example, socioeconomic status (SES) and education are potentially mediators of associations between mental disorders and physical health because of evidence that early onset mental disorders can influence subsequent SES trajectories,[27, 28] but they are also potential confounders of associations. Similarly, smoking is a potential mediator but it could also be a potential confounder if the initiation of smoking precedes the first onset of a given mental disorder. As a compromise, the multivariate model estimates are shown without and with adjustment for history of smoking (ever/never/current) and education (number of years). The next model additionally adjusted for all childhood adversities.

We investigated whether findings differed across countries by assessing whether there were interactions between any of the mental disorders and country income group (high versus low-middle income level). Of the 16 mental disorders included, the only one to show a significant interaction was binge eating disorder, with an interaction OR of 5.1 (1.7-14.8) indicating that the association between binge eating disorder and ulcer is stronger in countries with lower income levels. Because this was the only indication of differences in associations across countries, and because this specific interaction was accompanied by wide confidence intervals (due to the relatively small number of those with binge eating disorder in lower income countries), we report the results in this paper from models run on the pooled all-country dataset, with controls for country variation included in the models. In this context it is worth noting that our earlier studies of concurrent mental-physical comorbidity in the WMH surveys also found that these associations were generally consistent cross-nationally, despite substantial cross-national variation in the prevalences of mental disorders and physical conditions.[24] As the WMH data are both clustered and weighted, the design-based Taylor series linearization [29] implemented in version 10 of the SUDAAN software system was used to estimate standard errors and evaluate the statistical significance of coefficients.

RESULTS

Sample characteristics and history of ulcer diagnosis

Characteristics of the contributing surveys and prevalence of a self-reported history of ulcer diagnosis in the survey samples are shown in Table 1, with a total number of those reporting ulcer history of 3744.

Number of years between first onset of mental disorder and ulcer onset

Table 2 shows that the median number of years elapsing between mental disorder first onset and ulcer onset (the data in the 50th percentile column) ranged between 6 years for drug abuse and 20.6 years for specific phobia, with 7-10 years elapsing between first onset of most mental disorders and ulcer onset.

Type and number of mental disorders as predictors of ulcer onset

The first data column of Table 3 shows the results from bivariate models in which each mental disorder was modeled as a separate predictor of subsequent ulcer onset, without taking mental disorder comorbidity (or childhood adversities) into account. In these models all mental disorders were associated with ulcer, with ORs ranging from 1.8 to 3.2. The next column shows the results from a multivariate model that adjusted for mental disorder comorbidity. This reduced the magnitude of associations considerably, but depression, three of the anxiety disorders (social phobia, specific phobia and PTSD), intermittent explosive disorder and alcohol and drug abuse remained significantly associated with ulcer with ORs ranging from 1.3 to 1.7. The global chi square value for the joint effect of all mental disorders was large and highly significant (χ_{16}^2 = 434.9, p <=0.000) and the test for variation in the multivariate ORs was also significant (χ_{15}^2 = 38.5, p =0.0008). The significance of this latter test supports an interpretation of those mental disorders remaining significant in the multivariate model as having specific associations with ulcer (as opposed to just a generalized effect of psychological distress or psychopathology).

In the next model, adjustment for smoking history and education left some coefficients unchanged and others reduced slightly. The biggest difference it made was to the coefficients for substance abuse, where the estimate for alcohol abuse reduced from 1.5 to 1.3, and the estimate for drug abuse became insignificant.

Further adjustment for a wide range of childhood adversities in the final model slightly attenuated some associations but all mental disorders that had been significant in the prior model remained significant.

The models in Table 4 show the association between number of mental disorders and ulcer onset, regardless of type of mental disorder. In the first model there is a pronounced dose-response association with odds of ulcer diagnosis being 1.8 in those with one disorder and then increasing in a monotonic fashion to 4.3 in those with five or more lifetime disorders. These associations reduced in magnitude with adjustment for smoking and education, and then quite considerably further reduced with adjustment for childhood adversities.

DISCUSSION

These results need to be interpreted in light of the study's limitations. Retrospective assessment is known to lead to under-reporting of mental disorders [30] and inaccuracies in the age of onset timing for mental disorders,[31] although the version of the CIDI used in the WMH surveys has been modified to improve accuracy of age of onset reports. A further major limitation is the retrospective self-report of ulcer diagnosis.[32, 33] Both of these limitations are likely to have resulted in some misclassification of the predictor (mental disorder) and outcome (ulcer) variables. Where this misclassification is non-differential (i.e., independent) it is likely to have weakened associations. More of a concern is the possibility of differential misclassification through mental disorders at the time of interview affecting recall or report of ulcer; this kind of misclassification could inflate associations.[6] To examine this possibility we re-estimated the multivariate type model after excluding all those who met criteria for any mental disorder in the 12 months up to and including the

month of interview. Associations remained identical, or increased, for 5/6 of the significant mental disorder predictors in the original multivariate model (results available on request). The OR for social phobia decreased from 1.4 to a non-significant 1.2. We conclude from this that with the possible exception of social phobia, the associations reported here are unlikely to be inflated by differential misclassification. It does however remain probable that they are attenuated by non-differential misclassification of either the predictor or outcome variables. Finally, the consideration of potential confounders/mediators in these analyses was limited to one indicator of socioeconomic status, and a one-item measure of smoking status.

The results of this study are broadly consistent (the specific differences are discussed below) with those of the earlier Goodwin et al. studies[7, 8] in that we found associations between mood and anxiety disorders and ulcer onset, associations that persisted after adjustment for other mental disorders (including alcohol related disorders), sociodemographic variables and smoking history. Our findings extend that prior research in three ways. First, our inclusion as predictors only those mental disorders that had first onset prior to ulcer onset, excluding those mental disorders that were concurrent with ulcer onset (or even, as noted above, concurrent with interview), suggests that mental disorders may be associated with increased risk of ulcer development, although this would need to be confirmed in prospective studiesThe focus in this study on temporally prior mental disorders probably also explains why the associations we report here are generally of a smaller magnitude (from 1.2-1.6) than those reported in the Goodwin et al. studies (where they range from 1.5-2.2). Second, we found that the associations between specific mental disorders and ulcer onset were only minimally reduced by adjustment for a history of childhood adversities. Although this does not preclude other confounding factors underlying these mental disorders-ulcer links, it does suggest that these links are not simply the result of a common early background of adverse circumstance. Third, we were able to consider a wider range of mental disorders than prior research. Our finding that intermittent explosive disorder was significantly associated with ulcer is interesting in the context of the prior finding from the Alameda County study that hostility was related to subsequent ulcer onset,[12] and earlier experimental studies finding associations between measures of impulsivity and anger and increased gastric acid secretion in duodenal ulcer patients (see [34] for review).

Despite the broad similarities between the findings of this study and those from earlier cross-sectional research, there are nonetheless some discrepancies. The focus in this study on only those mental disorders with reported onset prior to ulcer onset probably explains why the associations we report here are generally of a smaller magnitude (ranging from 1.2-1.6) than those reported in the Goodwin et al. studies (ranging from 1.5-2.2). The earlier studies report concurrent comorbidity: this reflects either the association between mental disorders and ulcer, or the association between ulcer and subsequent mental disorders, or both. This study, by contrast, reports associations that reflect only one part of that possible bi-directional relationship. The specific anxiety disorders that we found associated with ulcer onset (specific and social phobia, PTSD) also differed from those found significant in the Goodwin et al. studies (GAD and panic disorder). One obvious reason for part of this discrepancy is that the Goodwin et al studies did not include PTSD. We note that the significant association we found for PTSD is consistent with several other studies linking PTSD with ulcer, suggesting that it is reliable.[9-11] The other differences between this study and earlier studies in terms of which specific anxiety disorders were significantly associated with ulcer may reflect the fact that our comorbidity adjustment included a wider range of mental disorders (including PTSD) than prior research. It may also reflect the focus on temporally prior mental disorders in this study, or the different samples. Although the large multi-national sample and broad range of mental disorders included in this study offers

some reason to consider these findings reliable, this can only be confirmed in subsequent longitudinal research.

Although this study adds to the body of evidence suggesting links between anxiety disorders and ulcers, this study sheds no light on whether these links are causal. There are, however plausible, causal mechanisms. It is conceivable, for example, that the common mechanism linking all of the emotional disorders (mood, anxiety, anger) with ulcer is related to the dysregulation of the hypothalamic-pituitary-adrenal and sympathoadrenal stress response pathways that have been associated with depression and anxiety disorders.[35-37] This dysregulation has been found to affect immune system function as well as gastric function and secretions.[6, 38, 39] These neuroendocrinological and neuroimmunological abnormalities that are associated with emotional disorders may therefore influence risk of ulcer onset through alteration of biological vulnerability to ulceration and/or defense against causative agents such as *H pylori*.

Behavioral mediators may also link mental disorders with ulcer development, although the associations reported here have persisted after adjustment for smoking history and substance use disorders. Among the possible other behavioral mediators that we were not able to include adjustment for, one of the most important may be use of nonsteroidal anti-inflammatory medications. Although this is often viewed as a confounder of links between psychosocial factors and ulcer,[6] it may also be a mediator because mental disorders are associated with increased risk of onset of chronic pain conditions.[19] Diet is another possible behavioral mediator (or confounder), although it seems unlikely that it would play a major role in explaining the observed associations.

Alcohol abuse was associated with subsequent ulcer diagnosis in this study, but not alcohol dependence. This initially counter-intuitive result may reflect selection effects whereby the transition from alcohol abuse to alcohol dependence is accompanied by the development of physiological tolerance, which may also entail a gastrointestinal (GI) tract tolerance of alcohol. This selection into alcohol dependence of those whose GI tracts can withstand heavy alcohol consumption may then identify a group whose GI tracts are less vulnerable to ulcer development. However, this interpretation is speculative and would require confirmation in further research, preferably involving clinician-derived diagnoses of abuse versus dependence. The elevated risk of ulcer associated with alcohol abuse found in this study is consistent with some prior research on heavy alcohol consumption,[12, 40] although not all.[41] This inconsistency in past research may be in part because measures of heavy alcohol consumption do not distinguish between abuse and dependence, and also be due to the complex, non-linear association between alcohol consumption and ulcers.[42]

In conclusion, this study demonstrates associations between a wider range of mental disorders and ulcer onset than previously investigated, even when restricted to mental disorders occurring prior to the onset of ulcer. It also shows that these associations are robust to adjustment for a shared history of childhood adversity, and that they increase in magnitude with the greater number of mental disorders experienced. This study uses retrospective data so these findings await confirmation in longitudinal studies; moreover it cannot determine whether these associations reflect causal mechanisms. Causal links are however plausible in light of abnormalities in the physiological stress response associated with mental disorders. Even in medical diseases with clear biological etiology such as peptic ulcers, mental disorders may play a role in modulating vulnerability to or persistence of disease.

Acknowledgments

The World Health Organization World Mental Health (WMH) Survey Initiative is supported by the National Institute of Mental Health (NIMH; R01 MH070884), the John D. and Catherine T. MacArthur Foundation, the Pfizer Foundation, the US Public Health Service (R13-MH066849, R01-MH069864, and R01 DA016558), the Fogarty International Center (FIRCA R03-TW006481), the Pan American Health Organization, Eli Lilly and Company, Ortho-McNeil Pharmaceutical, GlaxoSmithKline, and Bristol-Myers Squibb. We thank the staff of the WMH Data Collection and Data Analysis Coordination Centres for assistance with instrumentation, fieldwork, and consultation on data analysis. The Colombian National Study of Mental Health (NSMH) was supported by the Ministry of Social Protection, with supplemental support from the Saldarriaga Concha Foundation. The European surveys were funded by the European Commission (Contracts QLG5-1999-01042; SANCO 2004123; EAHC 20081308), the Piedmont Region (Italy), Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spain (FIS 00/0028), Ministerio de Ciencia y Tecnología, Spain (SAF 2000-158-CE), Departament de Salut, Generalitat de Catalunya, Spain, Instituto de Salud Carlos III (CIBER CB06/02/0046, RETICS RD06/0011 REM-TAP), and other local agencies and by an unrestricted educational grant from GlaxoSmithKline. The World Mental Health Japan (WMHJ) Survey was supported by the Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H13-SHOGAI-023, H14-TOKUBETSU-026, H16-KOKORO-013) from the Japan Ministry of Health, Labour and Welfare. The Mexican National Comorbidity Survey (MNCS) was supported by The National Institute of Psychiatry Ramon de la Fuente (INPRFMDIES 4280) and by the National Council on Science and Technology (CONACyT-G30544- H), with supplemental support from the PanAmerican Health Organization (PAHO). The Peruvian World Mental Health Study was funded by the National Institute of Health of the Ministry of Health of Peru. The Polish project Epidemiology of Mental Health and Access to Care –EZOP Poland was carried out by the Institute of Psychiatry and Neurology in Warsaw in consortium with Department of Psychiatry - Medical University in Wroclaw and National Institute of Public Health-National Institute of Hygiene in Warsaw and in partnership with Psykiatrist Institut Vinderen – Universitet, Oslo. The project was funded by the Norwegian Financial Mechanism and the European Economic Area Mechanism as well as Polish Ministry of Health. No support from pharmaceutical industry neither other commercial sources was received. The Shenzhen Mental Health Survey is supported by the Shenzhen Bureau of Health and the Shenzhen Bureau of Science, Technology, and Information. Implementation of the Iraq Mental Health Survey (IMHS) and data entry were carried out by the staff of the Iraqi MOH and MOP with direct support from the Iraqi IMHS team with funding from both the Japanese and European Funds through United Nations Development Group Iraq Trust Fund (UNDG ITF). The Israel National Health Survey is funded by the Ministry of Health with support from the Israel National Institute for Health Policy and Health Services Research and the National Insurance Institute of Israel. Te Rau Hinengaro: The New Zealand Mental Health Survey (NZMHS) was supported by the New Zealand Ministry of Health, Alcohol Advisory Council, and the Health Research Council. The Portuguese Mental Health Study was carried out by the Department of Mental Health, Faculty of Medical Sciences, NOVA University of Lisbon, with collaboration of the Portuguese Catholic University, and was funded by Champalimaud Foundation, Gulbenkian Foundation, Foundation for Science and Technology (FCT) and Ministry of Health. The Romania WMH study projects “Policies in Mental Health Area” and “National Study regarding Mental Health and Services Use” were carried out by National School of Public Health & Health Services Management (former National Institute for Research & Development in Health, present National School of Public Health Management & Professional Development, Bucharest), with technical support of Metro Media Transilvania, the National Institute of Statistics – National Centre for Training in Statistics, SC. Cheyenne Services SRL, Statistics Netherlands and were funded by Ministry of Public Health (former Ministry of Health) with supplemental support of Eli Lilly Romania SRL. The US National Comorbidity Survey Replication (NCS-R) is supported by the National Institute of Mental Health (NIMH; U01-MH60220) with supplemental support from the National Institute of Drug Abuse (NIDA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Robert Wood Johnson Foundation (RWJF; Grant 044708), and the John W. Alden Trust. A complete list of all within-country and cross-national WMH publications can be found at http://www.hcp.med.harvard.edu/wmh/.

Additional Funding: Work on this paper was funded by a grant from the Health Research Council of New Zealand to Kate M Scott.

The funders had no input into the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript.

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Table 1

Characteristics of WMH samples and percent (and number) with self-reported history of peptic ulcer diagnosis

			Sample Size			Self-reported history of peptic ulcer Diagnosis	
Country	**Field Dates**	**Age Range**	**Part 1**	**Part 2 sub-sample**	**Response Rate (%)**	**Number Unweighted (N)**	**Weighted (%)**
Americas							
Colombia	2003	18-65	4426	2381	87.7	292	10.7
Mexico	2001-2	18-65	5782	2362	76.6	118	3.5
United States	2002-3	18+	9282	5692	70.9	664	9.4
Peru	2005-6	18-65	3930	1801	90.2	76	3.5
Asia and South Pacific							
Japan	2002-6	20+	4129	1682	55.1	226	11.5
PRC Shen Zhen	2006-7	18+	7132	2475	80.0	181	5.0
New Zealand	2003-4	18+	12790	7312	73.3	424	5.4
Europe							
Belgium	2001-2	18+	2419	1043	50.6	86	6.1
France	2001-2	18+	2894	1436	45.9	78	5.7
Germany	2002-3	18+	3555	1323	57.8	86	6.2
Italy	2001-2	18+	4712	1779	71.3	85	3.5
The Netherlands	2002-3	18+	2372	1094	56.4	67	4.2
Spain	2001-2	18+	5473	2121	78.6	128	5.2
Northern Ireland	2004-7	18+	4340	1986	68.4	118	4.9
Portugal	2008-9	18+	3849	2060	57.3	204	8.8
Romania	2005-6	18+	2357	2357	70.9	195	7.4
Poland	2010-11	18-64	10081	4000	50.4	162	3.1
Middle East							
Israel	2002-4	21+	4859	4859	72.6	398	7.9
Iraq	2006-7	18+	4332	4332	95.2	156	3.4
Weighted averaged response rate (%)					78.0		
Total sample size			98714	52095		3744	

Table 2

Number of years elapsing between year of first onset of temporally prior DSM-IV mental disorders and year of ulcer onset

Type of Mental Disorders	Distribution of number of years between mental disorder onset and ulcer onset		
	25th percentile	50th percentile	75th percentile
I. Mood disorders			
Major Depressive Episode/ Dysthymia	3.3	8.7	16.6
Bipolar Disorder (Broad)	2.6	6.7	16.1
II. Anxiety disorders			
Panic Disorder	4.1	9.5	17.9
Generalized Anxiety Disorder	4.0	9.2	17.4
Social Phobia	9.2	15.8	23.7
Specific Phobia	12.0	20.6	3°.3
Agoraphobia without Panic	5.6	14.0	18.3
Post-Traumatic Stress Disorder	4.8	11.7	21.9
Obsessive Compulsive Disorder	1.8	7.4	13.8
III. Impulse-control disorders			
Intermittent Explosive Disorder	6.9	11.2	16.8
Binge Eating Disorder	3.9	6.7	15.8
Bulimia Nervosa	3.7	9.1	17.5
IV. Substance disorders			
Alcohol Abuse	3.6	7.9	14.9
Alcohol Dependence with Abuse	3.6	7.6	15.0
Drug Abuse	2.6	6.0	10.4
Drug Dependence with Abuse	3.1	8.1	11.2

Table 3

Bivariate and multivariate associations (odds ratios) between first onset of DSM-IV mental disorders and subsequent ulcer onset

	Bivariate Models[1]		Multivariate Type Model[2]		Multivariate Type Model with additional adj for smoking history and education		Multivariate Type Model with additional adj for childhood adversities	
	OR	(95% CI.)	OR	(95% C.I.)	OR	(95% C.I.)	OR	(95% C.I.)
I. Mood disorders								
Major Depressive Episode/ Dysthymia	1.8*	(1.6-2.0)	1.3*	(1.1-1.5)	1.3*	(1.1-1.4)	1.2*	(1.1-1.4)
Bipolar Disorder (Broad)	2.2*	(1.7-2.8)	1.1	(0.9-1.5)	1.1	(0.8-1.5)	1.0	(0.8-1.4)
II. Anxiety disorders								
Panic Disorder	2.1*	(1.6-2.6)	1.2	(0.9-1.5)	1.1	(0.9-1.5)	1.1	(0.8-1.4)
Generalized Anxiety Disorder	1.7*	(1.4-2.0)	1.0	(0.8-1.1)	0.9	(0.8-1.1)	0.9	(0.7-1.1)
Social Phobia	2.1*	(1.8-2.5)	1.4*	(1.1-1.6)	1.4*	(1.1-1.6)	1.3*	(1.1-1.6)
Specific Phobia	2.1*	(1.8-2.4)	1.7*	(1.5-1.9)	1.6*	(1.4-1.9)	1.6*	(1.4-1.8)
Agoraphobia without Panic	2.0*	(1.4-2.8)	1.1	(0.7-1.6)	1.0	(0.7-1.5)	1.1	(0.7-1.5)
Post-Traumatic Stress Disorder	2.6*	(2.1-3.1)	1.7*	(1.4-2.1)	1.6*	(1.3-2.0)	1.5*	(1.2-1.8)
Obsessive Compulsive Disorder	2.3*	(1.3-4.0)	1.6	(0.9-2.8)	1.6	(0.9-2.8)	1.6	(0.9-2.8)
III. Impulse-control disorders								
Intermittent Explosive Disorder	2.2*	(1.7-2.8)	1.5*	(1.1-1.9)	1.5*	(1.1-1.9)	1.4*	(1.1-1.8)
Binge Eating Disorder	1.9*	(1.2-3.0)	1.2	(0.8-1.8)	1.2	(0.8-1.8)	1.1	(0.7-1.6)
Bulimia Nervosa	2.1*	(1.1-3.6)	0.9	(0.5-1.8)	0.9	(0.5-1.7)	0.7	(0.4-1.5)
IV. Substance disorders								
Alcohol Abuse	2.0*	(1.7-2.3)	1.5*	(1.2-1.8)	1.3*	(1.1-1.6)	1.3*	(1.1-1.6)
Alcohol Dependence with Abuse	2.4*	(1.9-2.9)	1.1	(0.8-1.4)	1.0	(0.8-1.4)	1.0	(0.7-1.3)
Drug Abuse	2.7*	(2.1-3.3)	1.4*	(1.0-2.0)	1.3	(1.0-1.9)	1.3	(0.9-1.8)
Drug Dependence with Abuse	3.2*	(2.5-4.2)	1.0	(0.7-1.5)	1.0	(0.7-1.5)	1.0	(0.7-1.5)
Joint effect of all types of disorders, χ^2_{16}				434.9*		313.6*		187.9*

	Bivariate Models[1]		Multivariate Type Model[2]		Multivariate Type Model with additional adj for smoking history and education		Multivariate Type Model with additional adj for childhood adversities	
	OR	**(95% CI.)**	**OR**	**(95% C.I.)**	**OR**	**(95% C.I.)**	**OR**	**(95% C.I.)**
Difference between types of disorders, χ^2_{15}				38.5*		38.3*		37.7*

*Significant at the 0.05 level, two-tailed test.

[1]Bivariate models: each mental disorder type was estimated as a predictor of ulcer onset in a separate discrete time survival model controlling for age cohorts, gender, person-year and country.

[2]Multivariate Type model: the model was estimated with dummy variables for all mental disorders entered simultaneously, including the controls specified above.

Table 4

Multivariate associations (odds ratios) between the number of DSM-IV mental disorders and subsequent onset of ulcer

	Multivariate Number Model[1]		Multivariate Number Model with additional adj for smoking history and education		Multivariate Number Model with additional adj for childhood adversities	
	OR	**(95% C.I.)**	**OR**	**(95% C.I.)**	**OR**	**(95% C.I.)**
I. Number of disorders						
Exactly 1 disorder	1.8*	(1.5-2.0)	1.7*	(1.5-1.9)	1.6*	(1.4-1.8)
Exactly 2 disorders	2.1*	(1.8-2.5)	2.0*	(1.7-2.4)	1.8*	(1.6-2.2)
Exactly 3 disorders	2.9*	(2.3-3.5)	2.7*	(2.1-3.3)	2.3*	(1.9-2.9)
Exactly 4 disorders	3.5*	(2.5-4.9)	3.2*	(2.3-4.4)	2.7*	(1.9-3.8)
5+ disorders	4.3*	(3.4-5.5)	3.6*	(2.8-4.7)	2.7*	(2.0-3.5)
Joint effect of number of disorders, χ^2_5		299.6*		224.6*		142.3**

*Significant at the 0.05 level, two-tailed test.

[1]Multivariate Number model: the model was estimated with dummy predictors for number of mental disorders without any information about type of mental disorders, controlling for age cohorts, gender, person-year and country.