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## Anxiety and Depressive Symptoms and Medical Illness Among Adults with Anxiety Disorders

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### Abstract

**Objective**—Anxiety is linked to a number of medical conditions, yet few studies have examined how symptom severity relates to medical comorbidity.

**Purpose**—The current study assessed associations between severity of anxiety and depression and presence of medical conditions in adults diagnosed with anxiety disorders.

**Method**—Nine-hundred eighty-nine patients diagnosed with panic, generalized anxiety, social anxiety, and posttraumatic stress disorders reported on the severity of anxiety and depressive symptoms and on diagnoses of 11 medical conditions.

**Results**—Severity of anxiety and depressive symptoms was strongly associated with having more medical conditions over and above control variables, and the association was as strong as that between BMI and disease. Odds of having asthma, heart disease, back problems, ulcer, migraine headache and eyesight difficulties also increased as anxiety and depressive symptom severity increased. Anxiety symptoms were independently associated with ulcer, whereas depressive symptoms were independently associated with heart disease, migraine, and eyesight difficulties.

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**Conclusions**—These findings add to a growing body of research linking anxiety disorders with physical health problems and indicate that anxiety and depressive symptoms deserve greater attention in their association with disease.

### Keywords

anxiety; depression; psychosomatics; health psychology; medical comorbidity

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Individuals with elevated anxiety are more likely than those without anxiety to have a wide array of medical conditions, including cardiovascular, autoimmune, and neurodegenerative diseases, and are at greater risk for early mortality (1–4). The association between anxiety disorders and disease is understudied compared to that of depression and disease (5), which is surprising given that anxiety disorders are the most prevalent psychological disorders, affecting 30% of the population (6). Anxiety can be successfully treated with psychotherapy and medication (e.g., 7,8), and successful anxiety treatment significantly improves physical functioning (9). There is a pressing need to better understand the extent to which anxiety is linked to poor health and to specific illnesses. The goal of the current study is to assess the association between anxiety and depressive symptom severity and medical comorbidity in a sample of patients diagnosed with anxiety disorders.

The presence of an anxiety disorder is associated with greater medical comorbidity. In a large community sample ( $N = 42,249$ ), people diagnosed with anxiety disorders were more likely to have a variety of medical conditions including obesity (OR 1.2), diabetes (OR 1.3), asthma (OR 1.6), hypertension (OR 1.7), arthritis (OR 1.7), ulcer (OR 1.9), back/neck problems (OR 2.0), heart disease (OR 2.0), headache (OR 2.3), and multiple pains (OR 2.3) (10). Other studies report that adults with anxiety disorders have increased prevalence or risk of peptic ulcer disease (11), hypertension (12), coronary heart disease (13), and diabetes (14), and in a study of older adults, eyesight deterioration was associated with an increase in anxiety symptoms (15).

Associations between anxiety and disease may be explained by underlying biological processes such as allostatic load (16), inflammation (17), hypothalamic-pituitary-adrenal reactivity (18), and other neuroendocrine responses (17). Equally plausible is that having a medical condition leads to increased anxiety due to consequences of or discomfort associated with the condition. Bidirectional relations between anxiety and disease are likely.

Anxiety and depressive disorders are highly comorbid and their symptoms overlap (19). Therefore, it is important to assess whether links between anxiety and medical conditions are explained by overlap between anxiety and depression or whether anxiety contributes uniquely to medical comorbidity. Studies reveal unique contributions of anxiety to medical comorbidity over and above depression. For example, anxiety was a unique predictor of cardiac rehospitalization and prognosis over and above depression (20). Depression and anxiety disorders each uniquely contributed to risk for cardiac events in a longitudinal study (13). Comorbid anxiety and depression were associated with increased likelihood of medical disease presence relative to either disorder alone in one study (10) but not in another (13). These studies suggest that anxiety and depression are independently associated with medical

comorbidity, but it is unclear whether having comorbid anxiety and depressive disorders confers greater risk.

Although it is clear that medical conditions are more prevalent among patients with anxiety disorders compared to those without anxiety disorders, the current body of research has a number of limitations. First, to our knowledge, no studies have examined how the severity of anxiety and depressive symptoms relates to the presence of physical illness among individuals with anxiety disorders. Although causality cannot be inferred, cross-sectional associations between anxiety and depressive symptom severity and medical illness can elucidate whether there is a dose response relationship between disorder severity and disease risk. Second, among studies that have examined anxiety in the context of medical disease, most have examined only one medical condition at a time (11,14,21). This approach limits understanding of how anxiety relates to multiple medical conditions within the same sample. Third, the majority of studies have assessed anxiety and depressive symptoms using self-report measures in the absence of independent diagnostic evaluations. Thus, knowledge of disorder-level anxiety and depression comorbidity and its relation to medical conditions is limited.

The current study sought to fill these gaps using a convenience sample of patients diagnosed with anxiety disorders enrolled in the coordinated anxiety learning and management (CALM) treatment study. Results have been published from this sample showing higher levels of anxiety symptoms in patients with two or more medical conditions compared to those with no medical conditions (22). The current study builds on this finding by examining the strength of the association between anxiety and depressive symptoms with number of medical conditions controlling for demographic and health behaviors. In addition, the association between severity of anxiety and depressive symptoms with specific medical conditions including asthma, diabetes, hypertension, arthritis, heart disease, back problems, ulcer, inflamed bowel, thyroid disease, migraine, and eyesight difficulties was examined. The study had three aims. The first was to assess whether comorbidity of anxiety and depressive disorders was associated with higher overall and specific disease presence. The second was to assess whether greater severity of anxiety and depressive symptoms was associated with higher overall disease rates and presence of specific diseases. The third was to assess unique contributions of anxiety and depressive symptoms to disease rates and specific diseases.

## Method

### Participants

Participants were 989 primary care patients between the ages of 18 and 75 (see Table 1 for demographics). Between June 2006 and April 2008, 1620 primary care patients consented to complete a study eligibility interview, and 1004 patients with panic disorder (with or without agoraphobia), generalized anxiety disorder, social anxiety disorder, or posttraumatic stress disorder were enrolled. Fifteen participants had missing data on the variables of interest for the current study and were excluded from analyses. Participating research institutions were: University of Washington (Seattle), University of California-Los Angeles,

University of California-San Diego, University of Arkansas for Medical Sciences, and the RAND Corporation (an assessment site only). Details are presented elsewhere (23).

**Recruitment**—Primary care providers (PCPs) and clinic nursing staff directly referred potential participants. At some sites, a five-question anxiety screener, the Overall Anxiety Severity and Impairment Scale (OASIS; 24) was used to identify potential participants. A trained study clinician, the Anxiety Clinical Specialist (ACS), functioned as the diagnostician who met with referred patients to determine eligibility. All participants gave informed written consent to participate in this study, which was approved by each institution's Institutional Review Board.

**Inclusion Criteria**—An eligible participant had to be a patient at a participating clinic, 18–75 years old, meet DSM-IV criteria for one or more of panic disorder, generalized anxiety disorder, social anxiety disorder, or posttraumatic stress disorder based on the Mini-International Neuropsychiatric Interview (25) administered by the ACS (after formal training and diagnostic reliability testing), and score at least 8 (moderate and clinically significant anxiety symptoms on a scale ranging from 0–20) on the OASIS.

**Exclusion Criteria**—Patients with unstable or life-threatening medical conditions that could worsen and prevent consistent treatment adherence, marked cognitive impairment, active suicidal intent or plan, psychosis, or bipolar I disorder were excluded. Alcohol or marijuana abuse (but not dependence) was permitted, but other drug abuse or dependence was exclusionary. Patients already receiving ongoing CBT ( $n = 7$ ) were excluded, as were patients who could not speak English or Spanish ( $n = 2$ ).

## Procedure and Design

The current study analyzed data from only the baseline assessment time point of the larger treatment study. Therefore, the current study was cross-sectional in design and did not include data collected at follow-up time points. Following the baseline assessment, participants were randomized using stratified (by clinic and presence of co-morbid major depression) permuted block randomization, to the intervention group (ITV; including CBT, medication recommendations, or both) or the usual care group (UC) by an automated program at RAND. The baseline assessment was completed over the phone (as were subsequent assessments not analyzed here) by the RAND Survey Research Group. Further details regarding the study design and procedure are presented elsewhere (23). Further details are available about patient flow from referral through eligibility screening, consent, randomization and treatment effects (8).

## Measures

**Control variables**—Given that demographic factors and health behaviors are linked to disease, control variables were included in analyses.

**Demographics:** Age, gender, ethnicity (Caucasian, Hispanic, Black, or Other), education level (< 12 years, 12 years, > 12 years), and marital status (single or married/living together) were assessed via a self-report questionnaire.

**General health factors and behaviors:** Health-related variables and behaviors were assessed via self-report, including alcohol use frequency measured by average number of drinks per week, number of drinks on a typical drinking day, and frequency of binge drinking (> 6 drinks on one occasion), smoker status (assessed by < or > 100 cigarettes smoked in one's lifetime), exercise frequency (assessed with a four-point scale from "never" to "regularly"), and height and weight to determine body mass index (BMI).

### **Psychological diagnoses and symptoms**

**Mini-International Diagnostic Interview (M.I.N.I.):** The M.I.N.I. (25) is a 120-item fully-structured diagnostic interview that assesses seventeen disorders based on DSM-IV and ICD-10 criteria. Inter-rater (Kappa .88–1.00) and test-retest (Kappa .76–.93) reliability are very good (25).

**Psychological comorbidity:** Based on diagnoses from the M.I.N.I., participants were separated into four categories: one anxiety diagnosis (n = 161), multiple anxiety diagnoses (n = 149), one anxiety diagnosis and a depression or dysthymia diagnosis (n = 275), and multiple anxiety diagnoses and a depression or dysthymia diagnosis (n = 404).

**Brief Symptom Index – Anxiety subscale (BSI):** The BSI-18 (26) is a self-report 18-item measure assessing anxiety, somatic, and depressive symptoms. Items are rated on a 5-point Likert scale. Only the 6-item anxiety subscale was included in the current analyses as a general measure of anxiety. In the current sample, the mean was 10.1, the range was 0 (scale minimum) to 24 (scale maximum), and the standard deviation was 5.2. This measure has good psychometric properties (27). In the current sample,  $\alpha = .84$ . To aid in interpretation of the results and to provide an estimate of effect size, this scale was standardized with a mean of zero and a standard deviation of one.

**Patient Health Questionnaire – Depression (PHQ-9):** The PHQ-9 (28) is a 9-item self-report scale assessing depressive symptoms on a 4-point Likert-scale based on DSM-IV diagnostic criteria. In the current sample, the mean was 12.8, the range was 0 (scale minimum) to 27 (scale maximum), and the standard deviation was 6.3. It has demonstrated validity in the primary care setting (28) with excellent test-retest reliability (29). In the current sample  $\alpha = .85$ . To aid in interpretation of the results and to provide an estimate of effect size, this scale was standardized with a mean of zero and a standard deviation of one.

**Anxiety and depression symptom composite:** A composite of anxiety and depressive symptoms was created by averaging standardizing scores on the BSI and PHQ. The composite was created because there is significant overlap between anxiety and depressive symptoms ( $r = .56$  in the current sample), and in addition to unique contributions of anxiety and depressive symptoms, the association between an overall composite measure of symptom severity and medical comorbidity was of interest. In the current sample,  $\alpha = .89$ .

### **Dependent Variables**

**Specific medical conditions:** Medical conditions that are common causes of disability in the United States (30) were assessed during a phone interview in which interviewers asked,

“Has a doctor ever told you that you have any of the following?” Participants were then read 16 medical conditions and answered “yes” or “no” to each item. Of the 16 medical conditions, five were excluded from analyses due to insufficient sample sizes (kidney failure, chronic bronchitis, cancer, neurological conditions, stroke). Eleven were examined in the current analyses. These were presented to patients as follows: “asthma”, “high blood sugar or diabetes”, “hypertension or high blood pressure”, “arthritis or rheumatism”, “a heart attack, coronary heart disease, angina, congestive heart failure, or other heart disease”, “back problems including disk or spine”, “stomach ulcer”, “chronic inflamed bowel, enteritis, or colitis”, “thyroid disease”, “migraine headaches”, and “trouble seeing (even with glasses or contact lenses).”

**Total number of medical conditions:** The medical conditions endorsed were summed for each participant resulting in one score indicating the total number of medical conditions (range = 0–8). The correlation between patient-reported medical conditions and number of non-psychotropic medications prescribed was .541 ( $p < .001$ ), indicating that patient-reported medical conditions do index disease as recognized by the medical provider.

### Statistical Analyses

All analyses were conducted in Stata 12. Analyses were conducted on two types of dependent variables: number of medical conditions (a count variable) and presence or absence of each medical condition (dichotomous variables). Negative binomial regression with robust standard errors and logistic regression were used respectively. All analyses controlled for age, gender, ethnicity, education level, marital status, alcohol use frequency, BMI, smoker status, and exercise frequency. Three independent variables were examined. The association between psychological comorbidity category (one anxiety diagnosis, multiple anxiety diagnoses, one anxiety diagnosis and a mood disorder diagnosis, and multiple anxiety diagnoses and a depression or dysthymia diagnosis) and medical conditions was assessed. Next, the association between the anxiety/depression symptom composite and medical conditions was assessed. Finally, the association between anxiety and depression separately, each controlling for the other, on medical conditions was assessed.

## Results

### Association Between Control Variables and Medical Conditions

The association between the control variables and number of medical conditions was assessed using multiple linear regression. Control variables were age, gender, ethnicity, education level, marital status, alcohol use, BMI, cigarette smoker and frequency of exercise. Older age ( $p < .001$ ), being African American ( $p < .001$ ) or Caucasian ( $p = .025$ ) compared to Hispanic, less education ( $p < .001$ ), being single ( $p < .001$ ), less frequent alcohol use ( $p = .009$ ), higher BMI ( $p < .001$ ), and less exercise ( $p = .001$ ) were all significantly associated with having more medical conditions.

Next, the association between control variables and likelihood of having specific medical conditions was assessed using multiple logistic regression. All control variables with the exception of cigarette smoking were significantly associated with at least one medical

condition ( $ps < .05$ ), and older age and higher BMI were most frequently significantly associated with increased disease risk (10 out of 11 diseases for age and 6 out of 11 diseases for BMI). See Table 2 for associations between each predictor and specific diseases.

### Comorbid Psychological Diagnoses and Medical Conditions

**Total Medical Conditions**—Comorbidity of anxiety and depression was significantly associated with the number of medical conditions over and above all control variables ( $\chi^2 = 14.10, p = .003$ ) (see Figure 1). Tests of simple effects with a Bonferroni correction revealed that participants with multiple anxiety disorders and a comorbid depressive disorder had 1.3 times the number of medical conditions than participants with only one anxiety disorder (incidence-rate ratio; IRR = 1.27, 95% CI = 1.11 to 1.46,  $p = .001$ ). No other pair-wise comparisons were significant ( $ps > .082$ ).

**Specific Medical Conditions**—Comorbidity was associated with “trouble seeing” over and above all control variables ( $\chi^2 = 18.01, p < .001$ ). Tests of simple effects with a Bonferroni correction revealed that the odds of having difficulties with eyesight were 2.6 times larger for participants with multiple anxiety disorders and a comorbid depressive disorder than participants with multiple anxiety disorders and no depressive disorder (IRR = 2.58, 95% CI = 1.48 to 4.50,  $p = .001$ ). No other pairwise comparisons were significant ( $ps > .075$ ). Comorbidity was not associated with any other specific medical conditions ( $ps > .091$ ).

### Anxiety and Depression Symptom Composite and Medical Conditions

**Total Medical Conditions**—The symptom composite measure was significantly associated with number of medical conditions over and above all control variables (IRR = 1.15, CI = 1.10 to 1.20,  $p < .001$ ). For a one standard deviation increase in anxiety and depressive symptom severity, the estimated number of medical conditions increased by 15% (see Figure 2).

**Specific Medical Conditions**—The symptom composite was associated with increased presence of asthma ( $p = .039$ ), heart attack ( $p = .038$ ), back problems ( $p = .001$ ), ulcer ( $p = .001$ ), migraine ( $p = .011$ ), and eyesight difficulties ( $p < .001$ ). The associations between the symptom composite and diabetes, hypertension, arthritis, inflamed bowel diseases, and thyroid disease were not significant ( $ps > .051$ ). Odds ratios for all disease dependent variables are shown in Table 3.

### Unique Associations of Anxiety and Depressive Symptoms with Medical Conditions

**Total Medical Conditions**—Anxiety and depressive symptoms were each independently associated with total number of medical conditions over and above all control variables (Anxiety IRR = 1.06, CI = 1.00 to 1.11,  $p = .036$ ; Depression IRR = 1.11, CI = 1.06 to 1.17,  $p < .001$ ). For a one standard deviation increase in anxiety symptoms controlling for depressive symptoms, the number of medical conditions increased by 6%. For a one standard deviation increase in depressive symptoms controlling for anxiety symptoms, number of medical conditions increased by 11%. A post-hoc linear comparison revealed that the association between depressive symptoms and number of medical conditions was not

significantly stronger than that between anxiety symptoms and number of medical conditions (difference =  $-.06$ ; CI =  $-.15$  to  $.03$ ;  $p = .198$ ).

**Specific Medical Conditions**—Greater severity of anxiety symptoms after controlling for depressive symptoms was associated with increased likelihood of stomach ulcer ( $p = .021$ ), and greater severity of depressive symptoms after controlling for anxiety symptoms was associated with increased likelihood of heart attack ( $p = .021$ ), migraine ( $p = .004$ ), and eyesight difficulties ( $p < .001$ ). Results are shown in Table 3.

## Discussion

Compared to depression, the link between anxiety and physical health is relatively understudied. The current project examined how anxiety symptom severity and comorbidity with depression were associated with physical health in patients diagnosed with anxiety disorders. In all analyses, demographic (age, gender, marital status, ethnicity, and education) and health behaviors (BMI, smoking, exercise, and alcohol use) were controlled.

Although the current analyses do not allow us to infer causation, patients diagnosed with multiple anxiety disorders and depression also reported having more medical conditions than those diagnosed with only one anxiety disorder. This finding is consistent with previous research showing that patients with anxiety and depression have poorer physical health than patients diagnosed with either anxiety or depression alone (10). Thus, it is the patients with the highest levels of affect dysregulation who are showing the most overlap with medical illness. In addition, patients with multiple anxiety disorders and depression were more likely to endorse having eyesight difficulties than patients with multiple anxiety disorders and no depression. Although this analysis cannot inform directionality, perhaps vision impairment decreases one's ability to fully engage in enjoyable activities therefore increasing the likelihood of developing depression. Links between eyesight difficulties and psychopathology are discussed further below. Comorbidity was not associated with any other specific medical conditions suggesting that the effect of having multiple psychological disorders is more broadly linked to illness, but not specifically related to any one condition aside from eyesight difficulties.

Patients reporting more severe symptoms of anxiety and depression had more medical conditions. A one standard deviation increase in symptom severity was associated with a 15% increase in number of medical conditions. As a comparison, a one standard deviation increase in BMI was associated with a 12% increase in number of medical conditions. This finding is particularly striking given that the link between anxiety and depressive symptoms with illness was over and above that of demographics and health behaviors. In terms of specific medical diseases, severity of anxiety and depressive symptoms was related to higher rates of asthma, heart attack, back problems, ulcer and eyesight difficulties. Although the current findings do not inform directionality, they are consistent with a model recently proposed by O'Donovan, Slavich, Epel and Neylan (31), which links anxiety to diseases of aging such as cardiovascular, autoimmune, and neurodegenerative diseases. They review evidence that anxiety and early life stress increases inflammation through changes in the brain (3,32), changes in hypothalamic-pituitary-adrenal and autonomic nervous system

activity (33), and accelerated cellular aging (34). Given that anxious and depressed mood states increase symptom reporting (35), another possible explanation is that severity of anxiety and depressive symptoms is associated with increased symptom reporting and subsequent medical diagnosis by health care providers. The current study provides further evidence for a link between anxiety and medical comorbidity and shows a dose-response relationship between severity of anxiety and depressive symptoms and medical comorbidity.

Some specificity was evident between anxiety and depressive symptoms with particular diseases. Anxiety symptoms were independently linked to ulcers whereas depressive symptoms were independently linked to heart attack, migraine and eyesight difficulties. Research has revealed a strong relation between peptic ulcers and anxiety (11,36,37). In a recent paper, Collins, Surette and Bercik (38) reviewed the link between intestinal microbiota and the brain, suggesting that gut bacteria may have a direct effect on anxiety-like behavior in mice. They posit that this effect may explain high rates of comorbidity between psychiatric illness in patients with inflammatory bowel disease and ulcerative colitis.

Heart attack and migraine were uniquely associated with depression and not anxiety. Relations between depression and coronary heart disease (39), as well as depression and migraine headaches (40), have been clearly established. However, previous studies also have established a unique relation between migraine headaches and anxiety (41,42) as well as coronary heart disease events and anxiety (43). The discrepancy between current and prior findings may be due to the nature of our sample and type of measurement. Given that everyone in our sample was diagnosed with an anxiety disorder, the relation between anxiety symptom *severity* and migraine or heart attack presence was assessed. Perhaps these medical conditions are associated with anxiety presence only *or* are only associated with anxiety severity among non-diagnosed samples. Future research could examine an interaction effect of anxiety severity and diagnostic status on presence of these medical conditions.

Consistent with previous research, depressive symptoms were associated with eyesight problems. In a national survey of 10,480 adults living in the US, depression was significantly related to self-reported visual function loss (44). Proposed mechanisms are loss of valued activities, loss of mobility, fear of falling, anergia, changes in appetite, and sleep (45–47).

The current study has a number of limitations. All medical conditions were established via patient report of diagnoses. However, the validity of self-reported medical diagnoses is supported by significant links with number of non-psychotropic prescription medications taken and with control variables (e.g., age, ethnicity, education, marital status, BMI, exercise). Findings are mixed on whether patients are able to accurately report medical diagnoses (48,49), and future studies should replicate these findings with more objective measures, such as medical records. Second, these findings were not prospective, and thus directionality cannot be determined. However, links between psychological and physical illness are likely bidirectional, and research examining directionality and mechanisms could elucidate treatment and prevention implications. Finally, everyone in the current sample met

criteria for a current anxiety disorder and was interested in receiving treatment for an anxiety disorder. Without a control group or a group of patients uninterested in treatment, no conclusions can be drawn about relations among anxiety disorder presence and these medical conditions, and the generalizability of the effects are limited. Future research would benefit from examination of these relations among samples with anxiety disorders (with and without readiness to participate in anxiety treatment) compared to controls.

In conclusion, this study is the first to reveal that severity of anxiety and depressive symptoms in patients with anxiety disorders is associated with greater medical comorbidity. The association between anxiety and depressive symptoms with disease was as strong as the relationship between BMI and disease. In addition, anxiety symptoms were specifically related to ulcer whereas depressive symptoms were linked to heart disease, migraines, and eyesight difficulties. Although anxiety and depression evidenced significant overlap, they may contribute to diseases through distinct pathways, and the diseases are likely to carry distinct psychological consequences. Future research should examine biological, behavioral, and psychological mechanisms underlying the link between anxiety and depressive symptoms with medical illness to further elucidate the nature of this relationship. These findings add to the small data base linking anxiety disorders with medical illness and provide further evidence that clinicians may improve patient care by screening for and treating anxiety and depression in medically ill populations.

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## References

1. Carroll D, Phillips AC, Thomas GN, Gale CR, Deary I, Batty GD. Generalized anxiety disorder is associated with metabolic syndrome in the Vietnam experience study. *Biol Psychiatry*. 2009; 66(1): 91–3. [PubMed: 19344891]
2. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: The Framingham Offspring Study. *Psychosom Med*. 2005 Oct; 67(5):692–6. [PubMed: 16204425]
3. Li C, Barker L, Ford ES, Zhang X, Strine TW, Mokdad AH. Diabetes and anxiety in US adults: Findings from the 2006 Behavioral Risk Factor Surveillance System. *Diabet Med*. 2008; 25(7):878–81. [PubMed: 18644077]
4. Spitzer C, Barnow S, Völzke H, John U, Freyberger HJ, Grabe HJ. Trauma, posttraumatic stress disorder, and physical illness: findings from the general population. *Psychosom Med*. 2009 Nov; 71(9):1012–7. [PubMed: 19834051]
5. Miller G, Chen E, Cole SW. Health psychology: developing biologically plausible models linking the social world and physical health. *Annu Rev Psychol*. 2009; 60(1):501–24. [PubMed: 19035829]
6. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62(6):617–27. [PubMed: 15939839]
7. Craske MG, Stein MB, Sullivan G, Sherbourne C, Bystritsky A, Rose RD, et al. Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. *Arch Gen Psychiatry*. 2011; 68(4):378–88. [PubMed: 21464362]

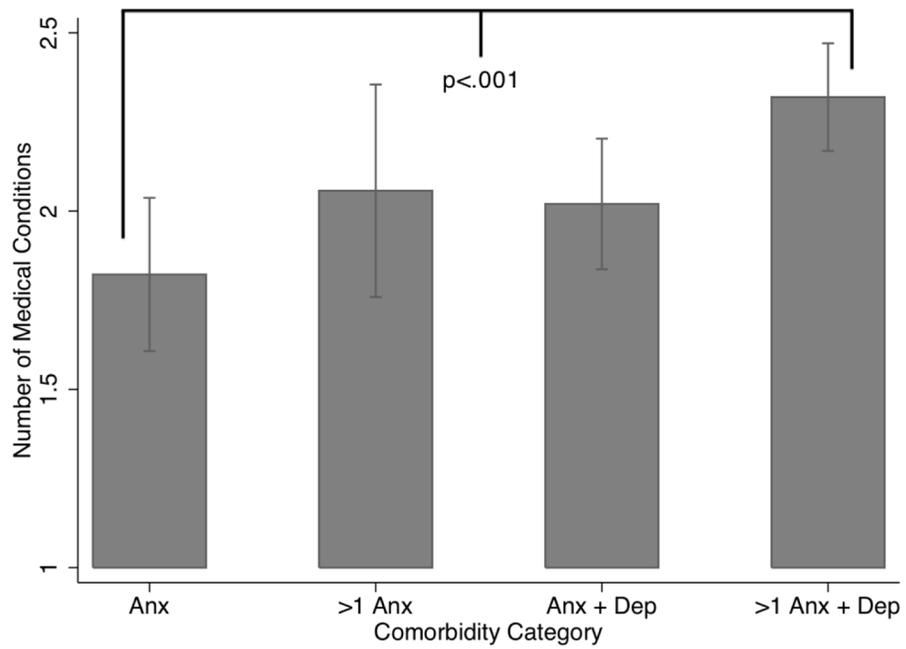
8. Roy-Byrne PP, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang AJ, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care. *J Am Med Assoc.* 2010; 303(19): 1921–8.
9. Niles AN, Sherbourne CD, Roy-Byrne PP, Stein MB, Sullivan G, Bystritsky A, et al. Anxiety treatment improves physical functioning with oblique scoring of the SF-12 Short Form Health Survey. *Gen Hosp Psychiatry.* 2013 Jun; 35(3):291–6. [PubMed: 23332608]
10. Scott KM, Bruffaerts R, Tsang A, Ormel J, Alonso J, Angermeyer MC, et al. Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. *J Affect Disord.* 2007 Nov; 103(1–3):113–20. [PubMed: 17292480]
11. Goodwin RD, Stein MB. Generalized anxiety disorder and peptic ulcer disease among adults in the United States. *Psychosom Med.* 2002 Dec; 64(6):862–6. [PubMed: 12461190]
12. Johannessen L, Strudsholm U, Foldager L, Munk-Jørgensen P. Increased risk of hypertension in patients with bipolar disorder and patients with anxiety compared to background population and patients with schizophrenia. *J Affect Disord.* 2006 Oct; 95(1–3):13–7. [PubMed: 16777235]
13. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *J Am Coll Cardiol.* 2010 Jun 29; 56(1):31–7. [PubMed: 20620714]
14. Atlantis E, Vogelzangs N, Cashman K, Penninx BJ. Common mental disorders associated with 2-year diabetes incidence: The Netherlands Study of Depression and Anxiety (NESDA). *J Affect Disord.* 2012; 142:S30–5. [PubMed: 23062854]
15. De Beurs E, Beekman AT, Deeg DJ, Van Dyck R, van Tilburg W. Predictors of change in anxiety symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. *Psychol Med.* 2000 May; 30(3):515–27. [PubMed: 10883708]
16. McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology.* 2000; 22(2):108–24. [PubMed: 10649824]
17. Pêgo JM, Sousa JC, Almeida OFX, Sousa N. Stress and the neuroendocrinology of anxiety disorders. *Curr Top Behav Neurosci.* 2010; 2:97–117. [PubMed: 21309108]
18. Risbrough VB, Stein MB. Role of corticotropin releasing factor in anxiety disorders: a translational research perspective. *Horm Behav.* 2006 Nov; 50(4):550–61. [PubMed: 16870185]
19. Kessler RC, Ormel J, Petukhova M, McLaughlin KA, Green JG, Russo LJ, et al. Development of lifetime comorbidity in the WHO World Mental Health (WMH) Surveys. *Arch Gen Psychiatry.* 2011 Jan; 68(1):90–100. [PubMed: 21199968]
20. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol.* 2003; 42(10):1801–7. [PubMed: 14642691]
21. Gore M, Sadosky A, Stacey BR, Tai K-S, Leslie D. The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. *Spine.* 2012 May 15; 37(11):E668–77. [PubMed: 22146287]
22. Campbell-Sills L, Stein MB, Sherbourne CD, Craske MG, Sullivan G, Golinelli D, et al. Effects of medical comorbidity on anxiety treatment outcomes in primary care. *Psychosom Med.* 2013 Oct; 75(8):713–20. [PubMed: 23886736]
23. Sullivan G, Craske MG, Sherbourne C, Edlund MJ, Rose RD, Golinelli D, et al. Design of the Coordinated Anxiety Learning and Management (CALM) study: innovations in collaborative care for anxiety disorders. *Gen Hosp Psychiatry.* 2007; 29(5):379–87. [PubMed: 17888803]
24. Campbell-Sills L, Norman SB, Craske MG, Sullivan G, Lang AJ, Chavira DA, et al. Validation of a brief measure of anxiety-related severity and impairment: The Overall Anxiety Severity and Impairment Scale (OASIS). *J Affect Disord.* 2009; 112(1–3):92–101. [PubMed: 18486238]
25. Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *Eur Psychiatry.* 1997; 12(5):224–31.
26. Derogatis, LR. BSI, Brief Symptom Inventory: Administration, scoring & procedures Manual. 4. Minneapolis, MN: National Computer Systems; 1993. p. 85

27. Meijer RR, de Vries RM, van Bruggen V. An evaluation of the brief symptom inventory-18 using item response theory: which items are most strongly related to psychological distress? *Psychol Assess.* 2011; 23(1):193. [PubMed: 21280957]
28. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001 Sep; 16(9):606–13. [PubMed: 11556941]
29. Löwe B, Kroenke K, Herzog W, Gräfe K. Measuring depression outcome with a brief self-report instrument: Sensitivity to change of the Patient Health Questionnaire (PHQ-9). *J Affect Disord.* 2004 Jul; 81(1):61–6. [PubMed: 15183601]
30. Centers for Disease Control & Prevention. Prevalence and most common causes of disability among adults: United States, 2005. *Morb Mortal Wkly Rep.* 2009; 58(16):421–6.
31. O'Donovan A, Slavich GM, Epel ES, Neylan TC. Exaggerated neurobiological sensitivity to threat as a mechanism linking anxiety with increased risk for diseases of aging. *Neurosci Biobehav Rev.* 2013 Jan; 37(1):96–108. [PubMed: 23127296]
32. Tottenham, N.; Sheridan, MA. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci* [Internet]. 2010 Jan 8. [cited 2013 Jun 28];3. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2813726/>
33. Maes M, Lin A, Bonaccorso S, van Hunsel F, Van Gastel A, Delmeire L, et al. Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. *Acta Psychiatr Scand.* 1998 Oct; 98(4):328–35. [PubMed: 9821456]
34. Okereke OI, Prescott J, Wong JYY, Han J, Rexrode KM, De Vivo I. High phobic anxiety is related to lower leukocyte telomere length in women. *PLoS ONE.* 2012 Jul 11.7(7):e40516. [PubMed: 22808180]
35. Bryant M, Suls J. The symptom perception hypothesis revised: Depression and anxiety play different roles in concurrent and retrospective physical symptom reporting. *J Pers Soc Psychol.* 2011; 100(1):182–95. [PubMed: 21219079]
36. Addolorato G, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Abenavoli L, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. *Int J Clin Pract.* 2008; 62(7): 1063–9. [PubMed: 18422970]
37. Goodwin RD, Talley NJ, Hotopf M, Cowles RA, Galea S, Jacobi F. A link between physician-diagnosed ulcer and anxiety disorders among adults. *Ann Epidemiol.* 2013 Apr; 23(4):189–92. [PubMed: 23453387]
38. Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. *Nat Rev Microbiol.* 2012 Nov; 10(11):735–42. [PubMed: 23000955]
39. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? a systematic quantitative review. *Psychosom Med.* 2003 Apr; 65(2):201–10. [PubMed: 12651987]
40. Bruti G, Magnotti MC, Iannetti G. Migraine and depression: bidirectional co-morbidities? *Neurol Sci.* 2012; 33(1):107–9. [PubMed: 21614579]
41. Baskin SM, Smitherman TA. Migraine and psychiatric disorders: comorbidities, mechanisms, and clinical applications. *Neurol Sci.* 2009 May 1; 30(1):61–5.
42. Merikangas KR, Angst J, Isler H. Migraine and psychopathology: results of the Zurich cohort study of young adults. *Arch Gen Psychiatry.* 1990 Sep; 47(9):849–53. [PubMed: 2393343]
43. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol.* 2010 Jun 29; 56(1):38–46. [PubMed: 20620715]
44. Zhang X, Bullard KM, Cotch MF, Wilson MR, Rovner BW, McGwin G, et al. Association between depression and functional vision loss in persons 20 years of age or older in the United States, NHANES 2005–2008. *JAMA Ophthalmol.* 2013 May 1; 131(5):573–81. [PubMed: 23471505]
45. Morse AR. Vision function, functional vision, and depression. *JAMA Ophthalmol.* 2013 May 1; 131(5):667–8. [PubMed: 23471550]
46. Rovner BW, Casten RJ, Tasman WS. Effect of depression on vision function in age-related macular degeneration. *Arch Ophthalmol.* 2002 Aug; 120(8):1041–4. [PubMed: 12149057]

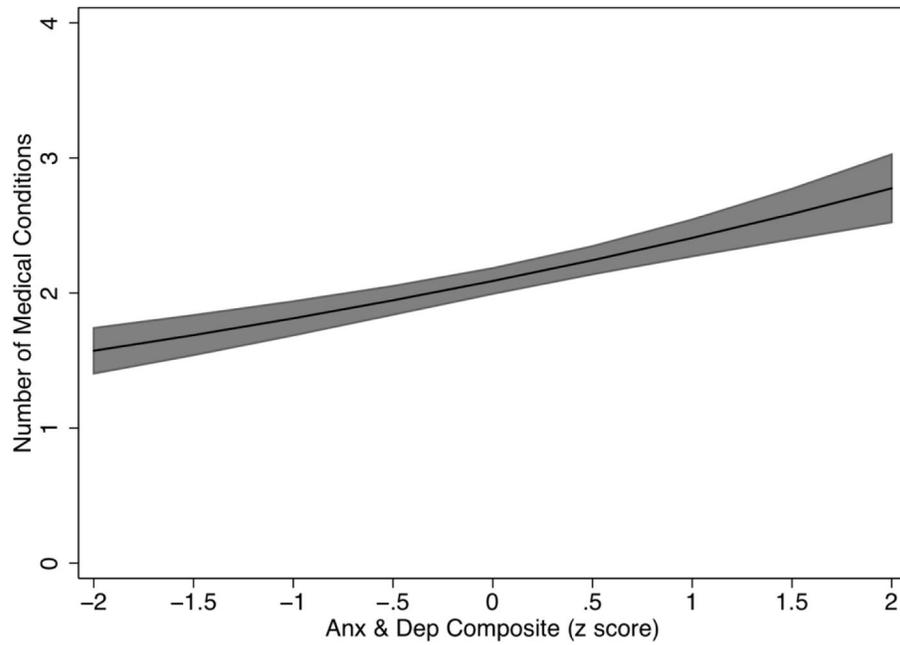
47. Rovner BW, Casten RJ. Activity loss and depression in age-related macular degeneration. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry*. 2002 Jun; 10(3):305–10.
48. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol*. 2004 Oct; 57(10):1096–103. [PubMed: 15528061]
49. Smith B, Chu LK, Smith TC, Amoroso PJ, Boyko EJ, Hooper TI, et al. Challenges of self-reported medical conditions and electronic medical records among members of a large military cohort. *BMC Med Res Methodol*. 2008 Jun 5.8(1):37. [PubMed: 18644098]

### Highlights

- Assessed link between anxiety disorder severity and medical illness
- Anxiety and depressive symptom severity strongly linked to medical comorbidity
- Symptom severity also linked to specific medical conditions
- Anxiety symptoms independently associated with ulcer
- Depressive symptoms linked to heart disease, migraine, and eyesight difficulties



**Figure 1.** Number of medical conditions by comorbidity category over and above control variables (age, gender, ethnicity, education, marital status, alcohol use, bmi, cigarette use, and exercise). Anx = one anxiety disorder, >1 Anx = multiple anxiety disorders, Anx + Dep = one anxiety disorder and comorbid depression, >1 Anx + Dep = multiple anxiety disorders and comorbid depression



**Figure 2.** Association between anxiety and depression composite and number of medical conditions over and above control variables (age, gender, ethnicity, education, marital status, alcohol use, bmi, cigarette use, and exercise) with a 95% confidence interval

**Table 1**

Characteristics of participants (n=989).

<b>Continuous Variables</b>	<b>Mean (SD)</b>
Age (years)	43.48 (13.5)
Body mass index (kg/m <sup>2</sup> )	28.14 (7.1)
<b>Categorical Variables</b>	<b>No. (%) of Patients</b>
Women	705 (71.3)
Education	
< High school	52 (5.3)
12 years	163 (16.5)
> 12 years	774 (78.3)
Race/ethnicity	
Hispanic	186 (18.8)
Black	115 (11.6)
White	565 (57.1)
Other	123 (12.4)
Married or living together	530 (53.6)
>100 cigarettes in lifetime	482 (48.7)
Alcohol use	216 (21.5)
Never	318 (32.2)
One night per week	254 (25.7)
2 nights per week	417 (42.2)
Exercise	
Regularly	430 (43.5)
Occasionally	289 (29.2)
Sometimes	216 (21.8)
Never	54 (5.5)
Number of medical conditions	
0	199 (20.1)
1	183 (18.5)
2	607 (61.4)
Anxiety disorders	
Panic	471 (47.6)
Generalized anxiety	745 (75.3)
Social phobia	398 (40.2)
Posttraumatic stress	176 (17.8)
Psychological comorbidity	
One anxiety dx	161 (16.3)
Multiple anxiety dx	149 (15.1)
One anxiety dx and a depression dx	275 (27.8)
Multiple anxiety dx and depression dx	404 (40.9)
Prescription psychotropic medication	625 (63.2)

Note. dx = diagnosis

Table 2

Regression analyses examining the relationship between control variables (age, gender, ethnicity, education, marital status, alcohol use, BMI, cigarette use, and exercise) and medical conditions

	Cons <sup>a</sup>	Age <sup>d</sup>	Gender (ref group = male)	Ethnicity (ref group = Caucasian)		Education	Marital Status	Alcohol use	BMI <sup>d</sup>	Cig	Exercise <sup>e</sup>
				Hisp	Black						
Negative Binomial Regression (b) <sup>b</sup>											
# Med Cond	.94	.33***	.10	-.15*	.15*	-.14***	-.17***	-.03**	.12***	.08	.08**
Logistic Regressions (Odds Ratio)											
Asthma	.82*	1.38	.72	1.21	.78	.75	.97	1.17*	1.20	1.00	
Diabetes	2.26***	.59*	1.27	2.40**	1.01	.67	.91	1.85***	1.14	.99	
Hypertension	2.04***	.52***	.74	2.31***	.94	.66**	1.00	1.71***	.83	1.28**	
Arthritis	3.47***	1.36	.51*	1.36	.69*	.78	.91*	1.39***	1.10	1.17	
Heart Disease	1.77***	.65	.21*	1.23	.55***	.93	.95	.92	1.47	1.32*	
Back Problems	1.66***	.99	.67	.78	.75*	.84	.93	1.24**	1.31	1.30***	
Ulcer	1.25*	1.24	1.00	.86	.70*	.67	.97	.98	1.09	1.10	
Inflamed Bowel	1.90***	1.60	1.13	.14**	.86	1.02	.89	.86	.97	1.10	
Thyroid	1.69***	5.91***	1.17	1.14	1.08	1.06	.86*	1.24*	1.43	.85	
Migraine	1.05	1.80***	.78	1.04	.87	.92	.98	.94	.93	1.12	
Eyesight	1.66***	1.24	1.17	2.18***	.73*	.58***	.98	1.12	1.23	1.10	

Note.

\*  $p < .05$ ;

\*\*  $p < .01$ ;

\*\*\*  $p < .001$ ;

cons=constant, ref group=reference group, BMI=body mass index, cig=cigarette use, Hisp=Hispanic, med cond=medical conditions

<sup>a</sup>Number of medical conditions of a single, Caucasian male with <12 years of education, no alcohol use in the past 6 months, <100 cigarettes smoked over lifetime, who exercises regularly, and with the average age and BMI of the sample

<sup>b</sup> $b$ =change in number of medical conditions for a one unit change in the predictor variable

<sup>c</sup>Higher numbers indicate less exercise

<sup>d</sup>z-scored variable in regression with mean=0 and standard deviation=1

**Table 3**

Associations between anxiety and depressive symptom composite (standardized) and various medical conditions, and unique associations between anxiety and depressive symptoms (standardized) and medical conditions

	Symptom Composite OR (95% CI)	Anxiety Symptoms OR (95% CI)	Depressive Symptoms OR (95% CI)
Asthma	1.18 (1.00–1.39)*	1.11 (.92–1.34)	1.09 (.90–1.32)
Diabetes	1.25 (1.00–1.58)	1.02 (.78–1.34)	1.27 (.96–1.69)
Hypertension	1.09 (.94–1.26)	1.17 (.98–1.40)	.93 (.78–1.12)
Arthritis	1.14 (.96–1.36)	.98 (.79–1.21)	1.19 (.96–1.48)
Heart Disease	1.33 (1.02–1.73)*	.94 (.68–1.29)	1.49 (1.06–2.10)*
Back Problems	1.29 (1.12–1.49)***	1.13 (.95–1.34)	1.18 (.99–1.41)
Ulcer	1.43 (1.16–1.78)***	1.34 (1.05–1.73)*	1.11 (.85–1.45)
Inflamed bowel	1.10 (.88–1.39)	.97 (.73–1.27)	1.16 (.88–1.53)
Thyroid	.99 (.77–1.26)	1.15 (.86–1.53)	.86 (.64–1.15)
Migraine	1.21 (1.04–1.40)*	.96 (.81–1.14)	1.29 (1.08–1.54)**
Eyesight	1.60 (1.36–1.89)***	1.17 (.97–1.42)	1.46 (1.20–1.78)***

Note:

\*  $p < .05$ ;

\*\*  $p < .01$ ;

\*\*\*  $p < .001$ ; Variables controlled for in all analyses include age, gender, ethnicity, education, marital status, alcohol use, BMI, cigarette use, and exercise