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BRIEF REPORTS

Feeling Bad in More Ways than One: Comorbidity Patterns of Medically Unexplained and Psychiatric Conditions

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BACKGROUND: Considerable overlap in symptoms and disease comorbidity has been noted among medically unexplained and psychiatric conditions seen in the primary care setting, such as chronic fatigue syndrome, low back pain, irritable bowel syndrome, chronic tension headache, fibromyalgia, temporomandibular joint disorder, major depression, panic attacks, and posttraumatic stress disorder.

OBJECTIVE: To examine interrelationships among these 9 conditions.

DESIGN: Using data from a cross-sectional survey, we described associations and used latent class analysis to investigate complex interrelationships.

PARTICIPANTS: 3,982 twins from the University of Washington Twin Registry.

MEASUREMENTS: Twins self-reported a doctor's diagnosis of the conditions.

RESULTS: Comorbidity among these 9 conditions far exceeded chance expectations; 31 of 36 associations were significant. Latent class analysis yielded a 4-class solution. *Class I* (2% prevalence) had high frequencies of each of the 9 conditions. *Class II* (8% prevalence) had high proportions of multiple psychiatric diagnoses. *Class III* (17% prevalence) participants reported high proportions of depression, low back pain, and headache. Participants in *class IV* (73% prevalence) were generally healthy. *Class I* participants had the poorest markers of health status.

CONCLUSIONS: These results support theories suggesting that medically unexplained conditions share a common etiology. Understanding patterns of comorbidity can help clinicians care for challenging patients.

KEY WORDS: primary care; fibromyalgia; chronic fatigue syndrome; back pain; depression.

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INTRODUCTION

Clinicians have long observed that some patients are burdened with a large number of medical complaints, and the challenge of caring for these patients has been acknowledged.[1] A subset of these patients has "medically unexplained" or "functional" conditions like chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia. Common psychiatric disorders such as major depression and anxiety are also frequently comorbid with these unexplained conditions but do not appear to fully explain them.[2] It has been proposed that the spectrum of unexplained conditions may reflect one underlying syndrome.[3]

We therefore examined the associations among 9 conditions usually considered medically unexplained or psychiatric—chronic fatigue syndrome, low back pain, irritable bowel syndrome, chronic tension headache, fibromyalgia, temporomandibular joint disorder, major depression, panic attacks, and posttraumatic stress disorder—using a community-based twin registry. The goals of this study were to (a) describe the associations among these conditions, (b) use latent class analysis (LCA) to investigate complex interrelationships between these conditions, and (c) describe the demographic and clinical characteristics of individuals falling within each class identified by LCA.

METHODS

Sample

All twins were participants in the University of Washington Twin Registry (UWTR), a community-based registry of twin pairs derived from applications for drivers' licenses in Washington State. The University of Washington receives lists of applicants who are twins, and each member of the pair is invited to join the UWTR and complete a health survey. Based on age and sex data for nonrespondents, registry participants are slightly younger and more likely to be female than the pool of potential twins. All UWTR procedures and the data collection involved in this study were approved by the University of

Table 1. Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals for 9 Conditions Evaluated Among Twins in the University of Washington Twin Registry

	Chronic fatigue syndrome	Low back pain	Irritable bowel syndrome	Chronic tension headache	Fibromyalgia	TMJ syndrome	Major depression	Panic attacks	Posttraumatic stress disorder
Chronic fatigue syndrome	–	4.8 (4.4–5.5)	4.2 (2.1–8.2)	11.5 (8.1–16.6)	38.6 (36.1–41.2)	4.8 (4.0–5.8)	10.6 (6.4–17.7)	6.0 (4.7–7.5)	9.4 (9.3–9.5)
Low back pain	4.2 (4.1–4.3)	–	3.0 (2.5–3.5)	2.8 (2.0–4.0)	7.5 (6.8–8.2)	2.4 (2.2–2.7)	3.3 (3.1–3.5)	2.8 (2.6–3.0)	3.4 (3.0–3.9)
Irritable bowel syndrome	3.2 (1.6–6.1)	2.1 (1.6–2.8)	–	2.6 (1.6–4.3)	2.6 (1.1–5.8)	1.5 (0.8–2.8)	1.7 (1.1–2.6)	1.6 (0.6–4.2)	2.3 (1.3–4.3)
Chronic tension headache	**10.7 (8.0–14.1)**	2.7 (2.0–3.6)	2.6 (1.7–3.9)	–	6.6 (6.6–6.7)	3.8 (3.4–4.2)	5.1 (4.5–5.8)	4.4 (3.8–5.0)	5.3 (4.6–6.1)
Fibromyalgia	**29.1 (26.9–31.5)**	**5.2 (4.4–5.9)**	1.7 (0.8–3.9)	**5.0 (4.3–5.7)**	–	10.4 (5.4–20.1)	6.1 (5.3–6.9)	4.2 (3.5–5.0)	9.0 (7.6–10.8)
TMJ syndrome	3.8 (3.4–4.2)	2.1 (1.8–2.3)	1.2 (0.6–2.3)	3.1 (2.6–3.7)	**7.0 (3.7–13.4)**	–	4.1 (4.1–4.2)	3.4 (2.4–4.8)	6.6 (6.2–7.1)
Major depression	**9.4 (5.2–16.8)**	3.2 (2.9–3.5)	1.6 (1.0–2.4)	4.5 (4.2–4.9)	4.6 (3.8–5.7)	3.4 (3.2–3.5)	–	14.0 (13.1–14.9)	20.3 (19.1–21.5)
Panic attacks	**5.1 (4.2–6.2)**	2.5 (2.4–2.6)	1.4 (0.5–4.2)	3.9 (3.6–4.1)	3.1 (2.7–3.6)	2.7 (1.8–4.2)	**12.7 (11.2–14.4)**	–	16.6 (12.2–22.6)
Posttraumatic stress disorder	**7.2 (6.9–8.0)**	2.8 (2.4–3.3)	1.6 (0.7–3.5)	4.7 (4.5–4.9)	**6.5 (5.6–7.6)**	**5.4 (4.8–5.9)**	**18.8 (17.0–20.8)**	**14.9 (10.8–20.5)**	–

Unadjusted odds ratios are above the diagonal; odds ratios adjusted for age and sex are shown below the diagonal. Pairwise comparisons were performed only on adjusted odds ratios. Strong to very strong associations (odds ratio of 5 or greater) are indicated in bold.
TMJ = temporomandibular joint

Washington Institutional Review Board. Informed consent was obtained from all twins.

Primary Measures

Nine conditions usually considered medically unexplained or psychiatric were chosen a priori for analyses. The presence of each condition was coded by the response to the question "Has your doctor ever told you that you have (specific condition)?" We chose this self-report method because diagnostic criteria for the conditions were not agreed upon or validated measures were unavailable or too lengthy for survey administration.

Demographics and Zygosity Assignment

Demographic characteristics were self-reported. We dichotomized race, marital status, education, and general health status and calculated body mass index (BMI; weight/height^2). Twins were asked about childhood similarity. Such questions classify zygosity with an accuracy of approximately 95% of that achieved with biological indicators.[4]

Statistical Analyses

Initial analyses were conducted with SAS v9.1 (SAS Institute Inc., 2004). Odds ratios (OR) and 95% confidence intervals were calculated as measures of association among all of the conditions. For all analyses, data from each individual twin were considered separately. We used generalized estimating equations to account for the nonindependence of twins and clustering of twins within a pair. For these initial analyses, age and sex were chosen as a priori covariates in the adjusted model. Pairwise comparisons were performed only on adjusted ORs.

Latent Class Analysis (LCA). Like cluster analyses, LCA[5] attempts to find groupings of individuals defined by responses to a number of items. We used LCA because it has yielded convergent results in prior studies of complex human traits[6] and is readily compatible with discrete data. We included all 9 conditions along with sex in the LCA.

To perform the LCA, we used FORTRAN with an efficient estimation-maximization algorithm[7] for maximum likelihood estimation. To determine the number of latent classes that gave rise to the observed data, we fit up to 10 latent class models to the data (50 separate runs with randomized starting values run for each to avoid the known problem of local minima). Number of classes was ascertained by using the Schwarz Bayesian criterion,[8] an index of parsimony that penalizes the goodness-of-fit statistic by the number of model parameters times the natural logarithm of the sample size. The Schwarz Bayesian criterion helps to determine the number of classes with a balance of goodness-of-fit and model complexity.

Demographic and Clinical Characteristics of Classes. We analyzed variables not entered into the LCA including age; marital status; education; medical, psychiatric, or alternative practitioner visits; total number of visits to a health professional; general health status; BMI; and exercise levels. We used Chi-square tests and linear regression to assess group differences among classes.

RESULTS

Participants

The sample included 1,042 monozygotic pairs, 828 dizygotic pairs, and 121 pairs of undetermined zygosity for a total of 3,982 individual twins. Of these, 3,937 had nonmissing data for all conditions and were included in the LCA. The mean age was 32.4 years (SD=14.7); 86% were white and 61% were female.

Associations Among the 9 Conditions

Table 1 presents unadjusted and adjusted ORs for all possible combinations of the 9 conditions. Strikingly, 31 of 36 comparisons performed were significant. At an alpha level of 0.05, we would expect approximately 2 associations to be significant by chance. Only irritable bowel syndrome had consistently low ORs.

Latent Class Analysis

The Schwarz Bayesian criterion declined for 1 to 4 class solutions, had minimal change for 5 classes, and then increased thereafter. Review of the solutions suggested that a 4-class solution best fit the data (see Table 2) and was more interpretable than the 5-class solution, as there was a clear minimum of the Schwarz Bayesian criterion.

Class I (2% of sample) had markedly high proportions of individuals who reported all of the 9 syndromes. *Class II* (8% of sample) participants had high proportions of multiple mental health conditions including major depression, panic attacks, and posttraumatic stress disorder, and low back pain. *Class III* (17% of sample) participants reported high proportions of depression, low back pain, and headache. *Class IV* (73% of sample) had the lowest proportion of females and low probabilities for all 9 conditions. There was poor agreement between class assignments for twin pairs (Cohen's kappa=0.1).

Demographic and Clinical Characteristics of Classes

Demographic and clinical characteristics of each class are presented in Table 2. The results suggest differences across groups, most notably between *class I* and *class IV. Class I* individuals most often reported fair or poor general health status and had the highest mean BMI, the highest total number of health care visits, and the lowest exercise frequencies.

DISCUSSION

We found consistent patterns of comorbidity between medically unexplained conditions in a community sample of twins. Two percent of our sample had high prevalences of all 9

Table 2. Latent Class Analysis Results for Sex and 9 Clinical Conditions with Demographic and Clinical Characteristics by Class

Item	Overall sample (*N*=3,937)	Class I (2%) multiplex	Class II (8%) depression and anxiety	Class III (17%) depression	Class IV (73%) unaffected	*P* value*
Variables in latent class analysis						
Female sex %	61	89↑	77↑	86↑	53	–
Low back pain %	27	91↑	47↑	47↑	19	–
Major depression %	20	85↑	97↑	53↑	2	–
Panic attacks %	12	55↑	92↑	9	3	–
Chronic tension headache %	8	49↑	20	30↑	1	–
Irritable bowel syndrome %	6	63↑	16	18	0	–
TMJ syndrome %	5	45↑	10	18	1	–
Posttraumatic stress disorder %	4	45↑	31↑	0	0	–
Chronic fatigue syndrome %	2	61↑	4	6	0	–
Fibromyalgia %	2	61↑	0	4	0	–
Demographic and clinical characteristics						
Married or living with partner %	40	51	42	50	37	<0.001
College education or more %	57	63	56	62	56	<0.010
Health fair or poor %	6	40	17	11	3	<0.001
Age in years, mean (SD)	32.3 (14.7)	35.7 (14.9)	42.4 (12.8)	34.9 (14.6)	31.1 (14.6)	<0.001
Psychiatric visits in past 3 months, mean (SD) and median	0.30 (1.9) 0	0.81 (2.1) 0	1.4 (3.8) 0	0.51 (2.2) 0	0.11 (1.4) 0	<0.001
Medical visits in past 3 months, mean (SD) and median	1.3 (3.0) 1	2.9 (4.9) 1	2.6 (6.9) 1	1.7 (2.6) 1	1.0 (2.2) 0	<0.001
Alternative practitioner visits in past 3 months, mean (SD) and median	0.68 (3.7) 0	2.3 (5.5) 0	1.6 (7.6) 0	0.81 (2.7) 0	0.5 (3.1) 0	<0.001
Total health visits in past 3 months, mean (SD) and median	2.4 (5.5) 1	6.0 (8.2) 3	5.6 (11.2) 2	3.1 (4.6) 1	1.6 (4.5) 1	<0.001
Body mass index, mean kg/m^2 (SD)	24.7 (5.1)	27.5 (6.9)	25.6 (6.4)	25.4 (5.7)	24.4 (4.7)	<0.001
Episodes of vigorous exercise per week, mean (SD)	1.4 (2.7)	0.77 (1.6)	1.1 (2.0)	1.0 (2.0)	1.6 (2.9)	0.115
Episodes of moderate exercise per week, mean (SD)	2.6 (4.1)	2.2 (3.8)	2.9 (7.1)	2.2 (2.6)	2.7 (3.9)	<0.001

To aid the reader, arrows indicate probabilities that deviate by ≥15% from the overall prevalence
**P values are for differences across all 4 classes*
TMJ = temporomandibular joint

conditions. Although depression and anxiety also commonly co-occurred with medically unexplained conditions, twins with predominantly mental health conditions appeared to be in distinct classes. Twins with a high burden of physical and mental illness were distinguished from healthy participants by their increased health care use, worse self-reported health status, higher BMI, and lower levels of physical exertion.

Our findings support proposals that a common pathway[9] or a single disease process[3] may underlie these clinically defined syndromes. The recent identification of candidate genes associated with chronic fatigue syndrome[10] could eventually reveal not only the physiological underpinnings of chronic fatigue, but common pathways for multiple currently unexplained syndromes.

Frequencies of medically unexplained syndromes were not markedly increased in the twins with the greatest psychiatric comorbidity and utilization of psychiatric care (*class II*). In contrast, the primary physical complaint was localized: low back pain. Again, localized symptoms of low back pain and headache predominated over medically unexplained syndromes in sufferers of depression alone (*class III*). These results concur with literature on both psychiatric comorbidity[11] and the association of mental health diagnoses with back pain[12] and chronic tension headache.[13] The comorbidity of mental illness and localized symptoms may reflect a limited ability to cope with common symptoms like headache or back pain in individuals with depression and anxiety. In sum, we found that twins with predominantly mental illness were distinct from those with the highest burden of medically unexplained syndromes, echoing prior findings.[14] For clinicians, these data reiterate the importance of screening for psychiatric conditions when painful or medically unexplained conditions are present.

This study was cross-sectional, thus limiting any conclusions about causality for the observed associations. In addition, the clinical conditions were assessed by single-item self-report of a doctor's diagnosis, which can be subject to response bias. However, our overall prevalences are comparable to available published general population rates for chronic fatigue syndrome,[15] low back pain,[16] fibromyalgia,[17] major depression,[11] panic, [18] and posttraumatic stress disorder.[19] Our use of self-report data may explain the lower-than-expected overall prevalence of irritable bowel syndrome, as research suggests that a large undiagnosed symptomatic population may exist.[20]

In summary, this study is unique in its use of a community-based sample of twins and diverse statistical approaches to examine patterns of comorbidity for 9 conditions seen in primary care. We defined a group with multiple medically unexplained syndromes who appeared to be distinct from individuals with primarily mental health diagnoses. Clinicians may find our results helpful for several reasons. First, they suggest individuals should be screened for comorbid disorders such as posttraumatic stress disorder when depression and anxiety are present and for major depression when low back pain and chronic headache are reported. Second, our findings also help clinicians understand that distressed patients are not merely accumulating diagnoses or somatic complaints, but have a constellation of conditions that frequently coexist, analogous to metabolic syndrome. Multiple medications for symptom management alone can be minimized, focusing instead on proven behavioral strategies such as graduated exercise or cognitive behavioral therapy. Finally, research seeking unified etiologies and treatment strategies is needed. Such ground-breaking work may eventually allow clinicians to feel confidence instead of consternation when treating patients with multiple unexplained, comorbid conditions.

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Conflict of Interest: *None disclosed.*

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