Health and Functional Status of Twins with Chronic Regional and Widespread Pain

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ABSTRACT. ***Objective.*** To examine the independent effects of chronic regional and widespread pain syndromes on health and functional status after accounting for comorbid chronic fatigue using a co-twin control design.

Methods. We identified 95 twin pairs discordant for pain in which one twin had chronic regional or widespread pain and the other denied chronic pain. Demographic data, functional and psychological status, health behaviors, and symptoms based on the 1994 criteria for chronic fatigue syndrome (CFS) were assessed by questionnaire. Psychiatric diagnoses were based on structured interview. Random effects regression modeling estimated associations between chronic regional and widespread pain and each health measure with and without adjustment for CFS.

Results. Significant differences ($p \leq 0.05$) were found within twin pairs discordant for chronic regional and widespread pain, for general health perception, and physical and mental health functioning as measured by summary scores from the Short Form-36. In addition, differences were observed within pain discordant pairs in psychological distress as measured by the General Health Questionnaire as well as the number of psychiatric diagnoses. Adjustment for CFS eliminated the association between chronic pain and mental health, but the association between chronic pain and poor general health, physical functioning, and sleep quality persisted ($p \leq 0.01$). Only the intra-pair difference in physical functioning distinguished twins with regional vs widespread pain ($p \leq 0.05$).

Conclusion. Both chronic regional and widespread pain exact debilitating effects on perceived general health, physical functioning, and sleep quality independent of CFS. However, the psychological and psychiatric influence of chronic pain appears closely tied to CFS. Research should examine the additive role of CFS-like illnesses in patients with chronic pain, and its influence on treatment and outcome. (J Rheumatol 2002;29:2426–34)

Key Indexing Terms:

TWINS	WIDESPREAD PAIN	REGIONAL PAIN
FIBROMYALGIA	CHRONIC FATIGUE SYNDROME	HEALTH STATUS

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Chronic widespread and regional pain syndromes affect roughly 4–10% and 20% of the general population, respectively[1-3]. Fibromyalgia (FM), a condition characterized by widespread pain[4], has a prevalence of 2% in the community[1]. There is growing recognition that tender points and widespread pain occur along a continuum both in the clinic[5] and in the general population[1,3,6]. Investigators have begun to question the practice of classifying pain syndromes as separate disease entities, suggesting this distinction may be artificial[5,7].

Features consistently associated with chronic widespread pain include high levels of functional impairment, psychological distress, and fatigue[1,8,9]. However, it is unknown if these features are unique to a particular illness such as FM or simply reflect the consequences of chronic pain[5,7,10,11]. Moreover, medical and psychiatric comorbidity may add to the substantial physical and mental impairment observed among patients with chronic pain. For example, FM often co-occurs with several unexplained clinical conditions such as chronic fatigue syndrome (CFS), irritable bowel syndrome, and temporomandibular disorder[1,9,12-16]. CFS has been independently associated with psychiatric morbidity[17],

poor health related quality of life[18], high levels of health care utilization, and work related impairments[19]. Although studies have shown that patients with comorbid FM and CFS report worse health status and function than those with only one condition[18-21], the degree to which CFS directly contributes to these negative health outcomes in chronic pain syndromes such as FM has yet to be quantified.

Historically, studies of FM have used patients with other rheumatic diseases or healthy volunteers as comparison groups, and few, if any, have adjusted for genetic or environmental factors. In this co-twin study, we examined twins discordant for either chronic regional or widespread pain consistent with the pain criteria for FM. This methodology provides excellent control for unrecognized genetic and environmental factors that may affect the characteristics of interest. Our objectives were to describe the relationship of regional and widespread chronic pain with functional status, psychiatric and psychological health, health habits, and behaviors, and to assess the effects of CFS on these domains.

MATERIALS AND METHODS

Subjects. Twins were identified for voluntary participation through national advertisements for twins with chronic pain and/or chronic fatigue. Sources of recruitment included support group newsletters (58%), notices on electronic bulletin boards (15%), clinicians and researchers familiar with FM or CFS (11%), twin organizations and researchers (6%), relatives and friends (3%), and other sources (7%). Each twin completed a comprehensive mailed questionnaire. The questionnaire included demographic information and a broad spectrum of physical and mental health measures (see below). In addition, medical records were requested from all participating twins. Zygosity was assigned using a validated self-report method[22,23]. The construction of this twin sample has been described[24]. Written, informed consent was obtained from each twin prior to participation.

Definition and validation of pain levels. All twins were asked a series of questions about chronic pain. Twins with chronic pain were identified by their response to the question: "Have you had pain on most days for the past 3 months?". For this study, only those twin pairs in which one twin responded "yes" and their co-twin responded "no" were included, thus creating a sample of chronic pain discordant twin pairs. Twins who endorsed the initial pain question were then asked to indicate in which of 8 possible body regions (chest, neck, lower back, upper back, right arm or hand, left arm or hand, right leg or foot, left leg or foot) they experienced chronic pain. Based on their distribution of pain, we defined 2 mutually exclusive groups of pain discordant twin pairs: those with chronic regional pain in at least one body region, and those with widespread chronic pain. The latter classification required that the location of the pain was bilateral, above and below the waist, and included an axial component such as the chest, neck, upper back, or lower back. This definition is consistent with the criteria for widespread pain characteristic of FM according to the American College of Rheumatology (ACR)[4].

To examine the validity of our pain classification system, medical records were abstracted by a research assistant blinded to participants' pain classification; subsequently, one of us independently (LAA) reviewed a random sample of 10% of all charts. Interrater agreement was 100% for any chart-documentation of FM. A diagnosis of FM was made in 65% of the twins classified with widespread pain compared to only 3% of co-twins classified as pain-free (kappa coefficient = 0.61). Moreover, individuals classified with chronic widespread pain were 2.7 times (95% CI 1.1–6.8) more likely to have a documented diagnosis of FM than twins with regional pain. These results provide support for the distinction between the 2 classification levels of widespread and regional pain used in this study.

Perception of health and functional status. We used the physical and mental health component summary scores[25] and the general health perception subscale from the Medical Outcome Study Short-Form 36 (SF-36)[26] to characterize health related functional status and perceived general health. The physical and mental health component scores have a mean of 50 and a standard deviation of 10 in the US population[25]. Scores on the general health perception subscale range from 0 to 100, and lower scores indicate worse perceived general health status[26]. The SF-36 subscales and composite scores have confirmed reliability and validity in diverse patient populations including those with chronic pain and fatigue[18,27-29].

Psychological distress and psychiatric disorders. The General Health Questionnaire (GHQ) was used to measure current psychological distress[30]. The GHQ contains somatic, severe depression, anxiety/insomnia, and social dysfunction subscales derived from factor analytic methods and a total distress score. All GHQ scores have confirmed acceptable reliability and concurrent validity[31].

To ascertain psychiatric conditions, the Diagnostic Interview Schedule Version III-A[32] was administered by telephone. This instrument is a structured interview that uses a computer algorithm to assign lifetime psychiatric diagnoses based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Version III-Revised[33]. A trained research assistant administered the sections on major depression, dysthymia, generalized anxiety disorder, panic disorder, agoraphobia, post-traumatic stress disorder, mania, bipolar disorders, schizophrenia, eating disorders, somatization, and alcohol and substance abuse/dependence, from which a total count of psychiatric diagnoses was derived. Telephone administration of the Diagnostic Interview Schedule has been validated in several large studies[34,35].

Health habits and behaviors. We examined several health related behaviors derived from questions included in the Registry questionnaire: regular exercise ("I exercise regularly"; 1 = never to 5 = always), sleep quality ("I often have a poor night's sleep"; 1 = never to 5 = always), caffeine use (cups of coffee or cans of cola per day), alcohol use (days in the past 2 weeks alcohol was consumed), cigarette use (number cigarettes per day). Body mass index was calculated as weight divided by the square of the person's height (kg/m^2). A threshold of > 27.3 for women and 27.8 for men was used to define obesity[36].

Chronic fatigue syndrome. Twins were classified as having CFS based on questionnaire responses and the structured psychiatric interview. As described in the 1994 Centers for Disease Control and Prevention case definition[37], CFS requires fatigue lasting ≥ 6 months, ≥ 4 of 8 specific symptoms, a body mass index < 45, and no exclusionary medical or psychiatric disorders. Psychiatric conditions exclusionary for the diagnosis of CFS included lifetime major depression with psychotic or melancholic features, mania, hypomania, bipolar disorder, schizophrenia, anorexia or bulimia nervosa, and current alcohol or substance abuse/dependence. A list of exclusionary medical diagnoses derived from a checklist in the Registry questionnaire was developed by consensus of 2 internists, a psychiatrist, an infectious disease specialist, and an emergency room physician. Examples of exclusionary conditions included (but were not limited to) steroid-dependent asthma, infectious hepatitis, diabetes, cancer, cirrhosis, and multiple sclerosis. To assess the accuracy of self-report data, self-reported conditions were compared to diagnoses obtained by chart review and communication with treating physicians for 44 twins. No fatigued twin had a condition exclusionary for CFS inaccurately obtained by self-report, and no exclusionary condition was observed in any twin who reported good health.

Statistical analyses. Our initial analysis examined the gender and zygosity distribution separately in chronic regional and widespread chronic pain discordant twin pairs; sociodemographic characteristics such as age, ethnicity, educational level, and marital and employment status also were examined. For descriptive purposes, we compared the total number of

painful body sites among twins with regional versus widespread pain only using the Wilcoxon sum rank test and provide the percentages of twins in each group with pain in particular body sites (e.g., neck, upper back).

For both regional and widespread pain discordant twin pairs, we then examined the association between chronic pain and each of the health status and functioning measures. Means or percents were used to present the basic comparisons of health measures in twins with and without pain. Formal statistical analysis involved the assessment of differences both within twin pairs (comparing twins with and without chronic pain) and between groups of twins (comparing intra-pair differences across the regional and widespread chronic pain groups). This approach allows us to assess the main effects of chronic pain and to detect if there are differential effects on functioning and health status that are uniquely dependent on the pattern of pain. Random-effects regression modeling procedures[38] that account for the paired structure of the data were used for statistical estimation and testing. Two regression models were constructed. In the first model, we tested the significance of within- and between-twin pair differences, after controlling for sociodemographic factors (age, sex, zygosity, educational level, and marital status). From this model we derived adjusted means (for continuous outcomes) or odds ratios (for binary outcomes) and their 95% confidence intervals. In the second model, we included all of the factors in the first model and added CFS status. This permitted us to determine the independent effects of both pain and CFS on health functioning and status. Of note, we conducted separate analyses that examined these data for differences on health measures according to zygosity; since both within- and between-pair effects were statistically equivalent for monozygotic and dizygotic twins, we have presented results pooled across zygosity. Analyses were conducted using SAS for Windows v. 6.12, Mixor v. 2, and Pepi Pairs v. 3[39-41].

RESULTS

Sociodemographic characteristics. Completed questionnaires were available for 221 twin pairs. Of these, 35 (16%) pairs were discordant for chronic regional pain and 60 (27%) pairs were discordant for chronic widespread pain. As shown in Table 1, the majority of these twins were monozygotic females. The twins' mean age was in their forties, they were predominantly Caucasian and married, and had some college education. Following adjustment for age, sex, education, zygosity, and marital status, twins with chronic widespread pain were less likely to be employed than their pain-free co-twins ($p \leq 0.01$), as were those with chronic regional pain ($p = 0.056$).

Pain characteristics. Twins with regional chronic pain had significantly fewer painful body regions than twins with chronic widespread pain (mean ± SE: 3.9 ± 0.2 vs 6.9 ± 0.1) out of a possible 8 body regions ($p \leq 0.0001$). The proportion of twins reporting pain at each site was lower among those with regional compared with widespread pain as follows: chest 43% vs 65%, neck 77% vs 90%, lower back 63% vs 78%, upper back 74% vs 93%, right arm or hand 17% vs 87%, left arm or hand 26% vs 95%, right leg or foot 49% vs 95%, and left leg or foot 43% vs 90%.

Health characteristics and functional status. Table 2 presents mean ± SE values of health and functional status characteristics in twin pairs discordant for chronic regional and widespread pain after adjustment for sociodemographic factors. With regard to perceived health and functional status, the SF-36 composite scores ranged from 32 (physical health) to 43 (mental health) among twins with chronic regional pain; values for the pain-free twins were higher, ranging from 48 (mental health) to 70 (general health). A similar pattern was noted among twins discordant for chronic widespread pain. Intra-pair differences for pain effects were statistically significant for all SF-36 subscales, indicating that twins with chronic pain, both regional and widespread, reported worse general health and functional status compared with their co-twins ($p \leq 0.001$). The magnitude of the intra-pair differences between chronic regional pain and widespread pain was not significantly different for either the general health or mental health composite ($p = 0.78$ and 0.72, respectively). However, the mean intra-pair difference for the physical health composite score among twins discordant for regional pain was significantly less than the difference in twins discordant for chronic widespread pain (19 vs 24; $p = 0.03$).

Table 1. Zygosity and demographic characteristics of chronic pain discordant twin pairs.

Characteristics	Chronic Regional Pain, n = 35		Chronic Widespread Pain, n = 60	
	Twins with Pain	Twins with No Pain	Twins with Pain	Twins with No Pain
Sex and Zygosity (%)				
Male-male monozygotic	2 (6)		1 (2)	
Female-female monozygotic	16 (45)		35 (58)	
Male-male dizygotic	1 (3)		2 (3)	
Female-female dizygotic	10 (29)		12 (20)	
Male-female dizygotic	6 (17)		10 (17)	
Demographic				
Age, mean yrs ± SE	42.2 ± 1.8		45.4 ± 1.2	
Ethnicity, % white	91		98	
Education, mean yrs ± SE	14.8 ± 0.6	15.1 ± 0.6	15.2 ± 0.5	14.9 ± 0.5
Married, %	54	60	63	75
Employed, %*	46	77	52	82

* Employment was higher among twins with no pain than twins with chronic regional ($p = 0.056$; OR 0.11, 95% CI 0.01–1.1) or widespread pain ($p = 0.0086$; OR 0.18, 95% CI 0.05–0.65).

Table 2. Functional status, mental health, and health behaviors in twins discordant for chronic regional and widespread pain adjusted for sociodemographic characteristics*.

Characteristic/Subscale	Range	Chronic Reginal Pain, n = 35		Chronic Widespread Pain, n = 60		Pain Effects	Regional vs Widespread Pain
		Twins with Pain	Twins with No Pain	Twins with Pain	Twins with No Pain	p	p
Health perception/functional status, mean score							
SF-36 general health	0–100	38.4 ± 3.8	70.0 ± 3.8	37.0 ± 3.1	77.2 ± 3.1	0.0001	0.78
SF-36 physical health composite	0–100	32.3 ± 1.6	50.9 ± 1.6	28.0 ± 1.3	52.0 ± 1.3	0.0001	0.03
SF-36 mental health composite	0–100	43.5 ± 1.9	48.5 ± 1.9	42.6 ± 1.5	49.2 ± 1.5	0.0002	0.72
Mental health indicators, mean score/number							
GHQ total	0–28	8.4 ± 1.0	2.9 ± 1.0	8.2 ± 0.8	2.9 ± 0.8	0.0001	0.88
Somatic symptoms	0–7	2.9 ± 0.3	0.9 ± 0.4	2.8 ± 0.3	1.0 ± 0.3	0.0001	0.88
Anxiety and insomnia	0–7	2.0 ± 0.3	0.9 ± 0.3	2.0 ± 0.3	1.2 ± 0.3	0.001	0.87
Social dysfunction	0–7	2.5 ± 0.3	0.9 ± 0.3	2.4 ± 0.3	0.5 ± 0.3	0.0001	0.80
Severe depression	0–7	1.0 ± 0.2	0.2 ± 0.2	0.9 ± 0.2	0.2 ± 0.2	0.0006	0.80
Lifetime psychiatric conditions†	0–7	1.2 ± 0.2	0.6 ± 0.2	1.1 ± 0.2	0.7 ± 0.2	0.0006	0.65
Health habits/behaviors							
Regular exercise**, rating	1–5	2.8 ± 0.2	2.8 ± 0.2	3.1 ± 0.2	3.1 ± 0.2	0.96	0.43
Caffeine, cups coffee/cola/day	2–10	3.7 ± 0.3	4.3 ± 0.3	3.2 ± 0.2	4.0 ± 0.2	0.0008	0.13
Alcohol, days used/past 2 wks	0–14	1.8 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	0.59	0.35
Cigarettes, number/day	3–40	16.6 ± 3.1	25.6 ± 3.0	21.7 ± 3.0	16.3 ± 2.9	0.32	0.30
Body mass index, kg/m^2	15.9–47.2	26.1 ± 0.9	24.7 ± 0.9	26.9 ± 0.8	25.1 ± 0.8	0.003	0.51
Poor sleep†† rating	1–5	3.5 ± 0.2	2.8 ± 0.2	3.7 ± 0.2	2.7 ± 0.2	0.001	0.46

* Means (± SE) adjusted for the effects of age, sex, zygosity, education, marital status.
† Lifetime psychiatric diagnoses obtained from structured interviews; those nonexclusionary for CFS are major depressive episode, depression not otherwise specified, dysthymia, somatization, panic disorder, generalized anxiety disorder, posttraumatic stress disorder. ** "I exercise regularly"; 1 = never to 5 = always. †† "I often have a poor night's sleep"; 1 = never to 5 = always.

Table 2 also shows the results for the psychological and psychiatric health status indicators adjusted for sociodemographic factors. Twins with chronic regional pain scored 8.4 (range 0–28) on the GHQ total score, with subscale score means ranging from 1.0 to 2.9 (range 0–7). This compared to a total mean GHQ score of 2.9 and GHQ subscale score ranging from 0.2 to 0.9 in pain-free co-twins. A similar pattern was observed among twins discordant for chronic widespread pain on the GHQ scales. Within-pair differences indicated that twins with chronic pain experienced more psychological distress (regardless of the type of distress) than their pain-free co-twins ($p \leq 0.001$). The magnitude of the intra-pair differences between twins with chronic regional pain and widespread pain did not differ for either the total GHQ (5.5 vs 5.3) or subscale scores ($p = 0.80$ to 0.88). Similarly, more lifetime psychiatric diagnoses were experienced by both twins with chronic regional pain (intra-pair differences 1.2 vs 0.6) and widespread pain (1.1 vs 0.7) compared to their pain-free co-twins ($p \leq 0.001$); however, the magnitude of the intra-pair difference did not differ significantly by pain type (0.6 vs 0.4, regional vs widespread pain; $p = 0.65$).

In terms of health behavior practices, intra-pair differences revealed that twins with chronic pain did not differ in regular exercise, consumption of alcoholic beverages, or cigarette use compared with their pain-free co-twins ($p = 0.32$ to 0.96). However, compared to pain-free twins, those with regional and widespread pain drank 0.6–0.8 *fewer* caffeinated beverages daily ($p \leq 0.001$), had worse sleep quality (mean difference 0.7–1.0; $p \leq 0.0001$), and had a higher body mass index (mean difference 1.4–1.8; $p \leq 0.01$). Finally, the magnitude of the intra-pair differences between twins with chronic regional pain and widespread pain did not differ for any of the health behaviors examined ($p = 0.13$ to 0.51).

Influence of CFS. Table 3 presents the results from an analysis of functional and health status indicators after adjusting for CFS. In general, the inclusion of CFS in the model reduced the effects of chronic pain. The most striking reductions in mean differences occurred in the mental health indicators. Specifically, intra-pair differences in the SF-36 mental health component score, the GHQ subscales measuring psychological distress, and the number of lifetime psychiatric diagnoses were no longer significant when CFS was included in the model with chronic pain. For example, without adjustment for CFS, twins with chronic regional pain had twice as many lifetime psychiatric diagnoses as pain-free co-twins (1.2 vs 0.6). However, when CFS was entered into the model (Table 3), the number of diagnoses was identical (0.7) in chronic regional pain and pain-free twins. A similar effect was observed in twins with widespread pain and their pain-free co-twins. In contrast, twins with chronic pain continued to exhibit markedly worse perceived general health, physical health functioning,

Table 3. Functional status, mental health, and health behaviors in twins discordant for chronic regional and widespread pain adjusted for sociodemographic characteristics and CFS*.

Characteristic	Range	Chronic Regional Pain, n = 35		Chronic Widespread Pain, n = 60		Pain Effects	Regional vs Widespread Pain
		Twins with Pain	Twins with No Pain	Twins with Pain	Twins wth No Pain	p	p
Health perception/functional status, mean score							
SF-36 general health	0–100	49.5 ± 3.8	65.3 ± 3.9	48.4 ± 3.3	69.2 ± 3.2	0.0001	0.81
SF-36 physical health composite	0–100	37.9 ± 1.7	49.7 ± 1.8	32.3 ± 1.5	49.4 ± 1.5	0.0001	0.01
SF-36 mental health composite	0–100	46.1 ± 2.1	49.5 ± 2.1	44.7 ± 1.8	49.1 ± 1.7	0.08	0.59
Mental health indicators, mean score/number							
GHQ	0–28	5.1 ± 1.1	3.3 ± 1.1	8.3 ± 1.3	3.7 ± 0.9	0.13	0.62
Somatic symptoms	0–7	1.8 ± 0.4	1.1 ± 0.4	2.1 ± 0.4	1.3 ± 0.3	0.11	0.45
Anxiety and insomnia	0–7	1.4 ± 0.4	1.0 ± 0.4	1.4 ± 0.3	1.2 ± 0.3	0.48	0.96
Social dysfunction	0–7	1.6 ± 0.4	1.1 ± 0.4	1.7 ± 0.3	0.8 ± 0.3	0.11	0.91
Severe depression	0–7	0.4 ± 0.2	0.2 ± 0.3	0.6 ± 0.2	0.3 ± 0.2	0.51	0.51
Lifetime psychiatric conditions†	0–7	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.6 ± 0.2	0.66	0.89
Health habits/behaviors							
Regular exercise**, rating	1–5	3.2 ± 0.3	2.9 ± 0.3	3.3 ± 0.3	2.8 ± 0.3	0.19	0.79
Caffeine, cups coffee/cola/day	2–10	3.5 ± 0.3	4.0 ± 0.3	3.1 ± 0.3	3.9 ± 0.3	0.08	0.30
Alcohol, days used/past 2 wks	0–14	1.8 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	0.19	0.25
Cigarettes, number/day	3–40	17.4 ± 3.2	25.4 ± 3.2	16.5 ± 3.2	18.8 ± 2.5	NE	NE
Body mass index, kg/m^2	15.9–47.2	25.5 ± 1.0	24.8 ± 1.1	26.0 ± 0.9	24.9 ± 0.9	0.38	0.70
Poor sleep††, rating	1–5	3.4 ± 0.2	2.9 ± 0.2	3.5 ± 0.2	2.6 ± 0.2	0.0076	0.79

* Means (± SE) adjusted for the effects of age, sex, zygosity, education, marital status, and CFS. † Lifetime psychiatric diagnoses obtained from structured interviews; those nonexclusionary for CFS are major depressive episode, depression not otherwise specified, dysthymia, somatization, panic disorder, generalized anxiety disorder, posttraumatic stress disorder. ** "I exercise regularly"; 1 = never to 5 = always. †† "I often have a poor night's sleep"; 1 = never to 5 = always. NE: not estimable.

and sleep quality compared to co-twins after adjustment for CFS ($p \leq 0.01$). After adjustment for CFS the only intra-pair difference between chronic regional and widespread pain was for the SF-36 physical health functioning subscale (11 vs 17; $p \leq 0.01$).

DISCUSSION

This co-twin control study observed an association between chronic pain and measures of function and health status. Compared to their pain-free co-twins, twins with both chronic regional and widespread pain were more likely to be unemployed, perceive their general health status and sleep as worse, and experience greater impairments in physical health. Although such features of poor health are well recognized among patients with chronic pain[8,10,20,42], the co-twin design provides evidence that these associations are likely attributable to pain per se rather than hereditary or shared familial/environmental influences.

Our results are consistent with studies showing an overall adverse effect on health perception as a consequence of chronic pain. Indeed, twins with both regional and widespread pain scored more than one standard deviation below the mean for the US population in general health perception[26] (49.5 and 48.4, respectively vs 71.9). Consistent with these results, a recent World Health Organization (WHO) study in primary care revealed that patients with pain present in at least one location on most days for 6 months or more was associated with unfavorable health perceptions compared to those without pain[42]. In this regard, disorders characterized by widespread chronic pain such as FM may be more correlated with poor general health status than other chronically painful conditions such as systemic lupus erythematosus or rheumatoid arthritis[1,43,44]. However, a recent study found no differences in perceived global health or level of dissatisfaction with health status in adults with FM and other chronic regional and widespread pain syndromes compared to those with comorbid FM and CFS[20]. It is possible that undetected comorbidity among individuals with FM has led to the conclusion that persons with FM have poor health perceptions.

In contrast, our results differ with some findings indicating that less extensive pain syndromes are correlated with better perceived health related quality of life[10,45]. For example, in a large random sample of Norwegian adults, individuals with widespread pain were more impaired on health related quality of life compared to those with regional pain syndromes[10]. However, differences in sampling (i.e., population vs clinic based), quality of life instrumentation,

and classification of pain syndromes may account for this discrepancy[7]. With regard to the latter, the Norwegian study defined regional pain as limited to the back or neck[10], while our comparable group averaged 3.9 painful sites occurring in any of 8 predefined areas of the body. Thus, our definition of regional pain may be more consistent with what has been termed "multifocal pain" by others[11,46].

We also found little evidence for a unique pattern of negative health effects based on a regional or widespread distribution of pain. Indeed, after adjustment for CFS, only the SF-36 physical health composite score differentiated twins with regional and widespread pain (37.9 vs 32.3). Nonetheless, twins with regional pain experienced significantly worse physical health than their pain-free counterparts, scoring more than one standard deviation below the mean of 50[25]. Similarly, in the WHO study, pain lasting 6 months, even if only in one location, imposed significant limitations on activities[42]. One-third of all the twins with chronic pain in this study experienced pain in only one anatomical site. Clearly, even limited chronic pain adversely affects physical health function; most likely, the extent and distribution of body pain are indicators of the severity of this impairment[5,7,11]. Moreover, among individuals with chronic widespread pain, physical health may be most impaired in those with FM.

Since many endogenous and exogenous events influence the central processing of nociceptive information[47], pain states are unlikely to be static and individuals may change categories (e.g., regional vs widespread) at various times. In support of this view, 2 prospective studies noted that individuals with more limited pain syndromes often developed extensive pain syndromes, such as FM[46,48]. Interestingly, only pain duration, number of painful sites, and pain occurring in the lower arm, but not the tender point count, predicted the development of either chronic widespread pain or FM in women with limited pain[46,48]. In another investigation, 28% of women initially diagnosed with FM no longer fulfilled criteria 5 years later, although most continued to experience chronic regional or multifocal pain[11]. Since persons with chronic widespread pain not fully meeting criteria for FM report a longer duration of pain, greater pain intensity, and more sleep problems than those with regional pain[49], they may be at an increased risk for developing FM. Taken together, these findings underscore the lack of information on the fluidity of pain states, the factors influencing change, and interventions that prevent the progression of pain and minimize its negative effect.

This study also clarifies the contribution of CFS to syndromes of chronic pain. We found that the adverse effects on mental health were largely attributable to CFS and not the pattern of pain. Specifically, comorbid CFS was associated with the number of psychiatric conditions, high levels of psychological distress, more social dysfunction, and poor mental health. Notably, the latter typically have been attributed to chronic widespread pain in both clinic and population based studies[1,7-9,42,50,51] and predicts the onset[52] and chronicity of pain[46,53]. However, an important limitation of these studies is that they did not adjust for chronic fatigue, which often co-occurs with chronic pain[20,21]. Indeed, the number of fatigue related symptoms has been reported to increase linearly with the distribution of bodily pain, being the highest among persons meeting full FM criteria[20]. Patients and community residents with comorbid FM and CFS also have been shown to rate their overall health as worse and have poorer physical and mental functioning, including more unemployment, than other groups with varying degrees of pain and fatigue[19,20,54]. Given that FM is characterized by greater fatigue than other rheumatological diagnoses[55], clinicians should routinely evaluate patients for comorbid fatiguing conditions such as CFS. Behaviorally based interventions including cognitive-behavioral and physical therapies shown to reduce the negative psychological (and physical) effects of chronic pain and chronic fatigue syndromes could then be applied to patients who present with such comorbidities.

The role of health behaviors in regional and widespread pain has been relatively neglected; this is unfortunate, since they are among the most readily modifiable risk factors for many chronic conditions[56]. We found that twins with regional or widespread pain were similar to their pain-free co-twins in frequency of regular exercise and use of cigarettes and alcohol. Of interest, in a recent twin study, the amount of self-reported exercise reduced the risk of joint pain in men, but not women, more than 2 decades later[57]. As our twins were predominantly female (85%), this may explain the lack of association between exercise and pain status. In contrast, twins with regional and widespread pain were significantly heavier, drank fewer caffeinated beverages, and slept more poorly than their pain-free co-twins. The association of sleep quality with any type of chronic pain in our sample is consistent with reports that poor sleep is a common feature of chronic pain in general[58], as well as of FM and CFS[59,60]. Although more severe sleep disturbances have been reported among persons with widespread than regional chronic pain[10,49], global sleep quality was similar in our twins with regional and widespread pain. This may have resulted from the lack of sensitivity of the single item we used to assess sleep quality. Nevertheless, educational[61], behavioral[62,63], and pharmacological interventions are justified in any patient with chronic pain who exhibits poor sleep quality.

One aspect of this study that deserves mention is our use of twins. Although co-twin control studies have identified immunological aberrations, environmental triggers, and behavioral risk factors in rheumatoid arthritis[64], osteoarthritis[65], and systemic lupus erythematosus[66], few have examined pain. To better understand the genetic origins of pain perception, a classical twin study used a single dolori-

metric measurement on the forehead in a volunteer sample of over 600 female twins[67]. Similar twin correlations in monozygotic and dizygotic twins suggested a trivial genetic influence on pain pressure threshold and a strong effect of common environment. However, the dolorimetric measures were taken with both members of a pair in the examining room at the same time, thus potentially artificially inflating both the monozygotic and dizygotic twin correlations. Similarly, in a recent study of temporomandibular disorder, a condition often linked with FM[14-16], monozygotic twins were no more similar than dizygotic twins[68], suggesting that genetic factors do not influence this trait. Environmental factors unique to each twin appeared to be the major determinants of phenotypic variation. In contrast, an investigation of back pain in a large twin registry provided evidence for a relationship with genetic factors[69]. In our own twin study, we adjusted for the effects of an environmental exposure factor, stressful life experiences, in the analyses reported in Tables 2 and 3 (data not shown), but did not observe any change in the reported outcomes. Thus, pain potentially may have both substantial genetic and environmental determinants, but the relative contribution of each may differ by the pain condition under examination. Given the paucity of studies in this area, this requires further investigation.

This study has several limitations. First, although our definition of chronic widespread pain closely followed the 1990 ACR criteria for FM, we were unable to verify the diagnosis of FM by physical examination. Nonetheless, we attempted to validate the adequacy of our classification system using chart reviews. Second, the diagnosis of CFS relied on self-reported health conditions rather than on a clinical examination. Thus, the term CFS-like, which is used when physical and laboratory examinations have not been conducted, more accurately defines the fatiguing illness in this study. Use of self-reported health conditions could result in misclassification depending on whether individuals failed to note exclusionary conditions or, alternatively, incorrectly reported conditions they did not have. Nonetheless, we presented evidence that the ascertainment of exclusionary medical conditions was adequate. Third, the method we used to identify the twin sample was not ideal. Solicitation by advertisement resulted in a volunteer sample of twin pairs, with the potential for ascertainment biases. Although we emphasized in recruitment efforts that probands were desired regardless of either the health of their co-twin or a definitive, clinical diagnosis of FM, it is possible that potential subjects screened themselves as either eligible or ineligible. Finally, although we evaluated one potential alternative explanation for our findings (i.e., whether stressful life experiences account for differences among pain vs pain-free co-twins), the co-twin control design cannot entirely eliminate the possibility that other unique environmental experiences influence the outcomes examined.

In summary, using a unique study design to adjust for genetic and environmental influences, we demonstrated that individuals with chronic pain experienced worse perceived health status, greater physical impairment, and poorer sleep quality than well matched, pain-free controls. These effects were observed in both regional and widespread pain syndromes, suggesting that chronic pain per se was responsible for the negative effects on health. This investigation is the first to report that the effects of chronic pain on general physical health and function are independent of CFS; conversely, effects on psychological health appear to be attributable primarily to comorbid CFS. Finally, there were few differences in health status and behaviors between pain discordant twins with regional and widespread pain. Therefore, patients with chronic pain should be assessed for comorbid CFS. Future research should examine the additive role of CFS-like illnesses in chronic pain and its influence on treatment and outcome.

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