The Relation of Physical Comorbidity and Multimorbidity to Fibromyalgia, Widespread Pain, and Fibromyalgia-related Variables

Frederick Wolfe, Jacob Ablin, Emma K. Guymer, Geoffrey O. Littlejohn, and Johannes J. Rasker

ABSTRACT. ***Objective.*** To investigate the relation of physical (non-psychological) comorbidity and multimorbidity to quantitative measures of fibromyalgia (FM) and musculoskeletal pain.

Methods. We studied 12,215 patients in a research databank with quantitative measures of FM-related variables (FMV) that included binary determinations of FM and widespread pain (WSP), and constituent variables of FM diagnosis that included the WSP index (WPI), the symptom severity score (SSS), and the polysymptomatic distress scale (PSD). We assessed self-reported comorbid conditions and covariates that included age, sex, body mass index, hypertension, smoking history, and total household income. We used nearest-neighbor matching and regression adjustment treatment effects models to measure the effect of comorbidities on FMV.

Results. We found a positive association between FMV and the probability of having each comorbid condition. Patients with ≥ 1 comorbidities had PSD, WPI, and SSS increases of 3.0 (95% CI 2.7–3.3), 1.8 (95% CI 1.6–2.0), and 1.2 (95% CI 1.1–1.3) units, respectively, and an increase in FM prevalence from 20.4% to 32.6%. As the number of comorbid conditions present increased from 1 to 4 or more, PSD, WPI, SSS, and FM percent increased stepwise. For patients with ≥ 4 conditions, the predicted prevalence of FM was 55.2%.

Conclusion. FM and FMV are associated with an increase in the number of comorbidities, and the association can be measured quantitatively. However, the association of WSP and FM may be an effect of definitions of WSP and FM, because comorbidity increases are also present with subsyndromal levels of both conditions. (First Release December 15 2019; J Rheumatol 2020;47:624–31; doi:10.3899/jrheum.190149)

Key Indexing Terms:
FIBROMYALGIA COMORBIDITY PAIN

Among the observed characteristics of fibromyalgia (FM) and widespread pain (FM&WSP) is their association with psychological[1,2] and physical (non-psychological) comorbid disorders[3,4,5,6,7,8]. Psychological disorders are increased in FM&WSP, and the relation between FM&WSP and psychological disorders is generally understood to be bidirectional regarding causation[9,10,11].

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Physical comorbid conditions are less well characterized, because associations with FM&WSP have not been established for more than a few conditions, and the mechanisms for the associations remain uncertain and unclear. Although "all diseases are more or less statistically associated with each other," according to Jakovljevic and Ostojic[12], the mechanisms by which cancer or neurological disorders, for example, are associated with FM and polysymptomatic distress scale (PSD) remain unknown[7]. Interest in complex systems and network models may offer future insights into FM&WSP issues[13,14].

To understand the FM-comorbidity association, quantitative data are required, including the measured risk of FM&WSP, given 1 or more comorbidities. Because the risk of FM&WSP is dependent on the level of and change in FM criteria–related variables (FMV)[15,16], including the WSP index (WPI), the symptom severity scale (SSS), and the PSD, risk should also be measured as a function of these FMV with and without comorbidity presence.

One idea relating to the causation of FM is that it "reflects a distressed organism where the sources of distress may be multiple," as Cohen and Quintner[17] put it. We hypothesize

that one such stressor is comorbid disease. We examine the data from the causal perspective that comorbid disease influences the risk of FM and change in FMV. From these data, we measure the risk of FM and change in FMV associated with comorbidity. Such data should also provide useful information that relate to causal pathways in FM&WSP development and severity.

MATERIALS AND METHODS

Patients. We used data from persons participating in the National Data Bank for Rheumatic Diseases (NDB) study of longitudinal outcomes to investigate the relation of comorbid disease to FM diagnosis and FM-related variables. Data from semiannual self-report questionnaires were collected from 2009, the time that FM criteria variables first became available in the NDB, through 2014. Because patients may have had many semiannual observations during this period, we randomly selected 1 observation per patient for inclusion in the study. The characteristics of the NDB have been reported previously[18,19]. In our study, we identified 2 diagnostic groups of patients with pain, 9017 patients with rheumatoid arthritis (RA) and 3198 referred with noninflammatory rheumatic and musculoskeletal disorders (NIRMD), including FM, osteoarthritis, and back pain syndromes. The clinical rheumatic disease diagnoses were made by the patient's rheumatologist or confirmed by the patient's physician. We combined the data from the 2 groups to form a single dataset composed of 12,215 patients. We have recently reported that primary and secondary FM are effectively the same regarding diagnosis and outcomes[20].

Outcome variables. The outcome variables were FM diagnosis by 2016 modified American College of Rheumatology (ACR) criteria[16], and 3 component variables of the 2016 criteria: the WPI, the SSS, and the PSD. The WPI (0–19) is a summary count of the number of painful regions from the Regional Pain Scale, a self-reported list of painful regions[21]. The SSS (0–12) is the sum of the severity scores of 3 (0–3) symptoms (fatigue, waking unrefreshed, and cognitive symptoms; 0–9) plus the sum (0–3) of the number of the following symptoms the patient has had during the previous 6 months: headaches (0–1), pain or cramps in lower abdomen (0–1), and depression (0–1). The PSD (0–31) is the sum of the WPI and SSS. The PSD measures the magnitude and severity of FM symptoms in those satisfying and not satisfying criteria. By definition, FM criteria cannot be satisfied if the PSD is < 12. We identified WSP using the definition of the 1990 ACR FM criteria[22]: "Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present." We also calculated the WSP definition of the 2016 FM criteria revision[16].

Comorbidity variables. In a section in the study questionnaire labeled "Current Health Problems," patients were asked to check a box if they had the problems listed in the last 6 months. Problems were characterized singly or combined into 12 variables that were used for analysis: (1) diabetes; (2) gastrointestinal (GI): liver, ulcers, or gall bladder problems; (3) pulmonary: lung problems or asthma; (4) psychological: depression, mental illness, alcohol or drug abuse; (5) stroke; (6) fractures of spine, hip, or leg; (7) cataracts; (8) genitourinary (GU): problems with prostate (men), or uterus, ovaries, etc. (women); (9) renal: kidney problem; (10) cancer; (11) neurological (seizures, Parkinson's disease, multiple sclerosis, etc.); (12) heart: heart attack or other heart problem. In another section of the questionnaire, relating to symptoms, we asked patients if they had irritable bowel syndrome (IBS).

Other study variables. To categorize patients' characteristics and for use as covariates (Table 1), we collected data on age, sex, total household income, education, body mass index (BMI), FM diagnosis, WPI, SSS, PSD, WSP, visual analog score (VAS) pain, and the physical and mental components of the Medical Outcomes Study Short Form-36 questionnaire (SF-36).

Table 1. Demographic and clinical characteristics of the National Data Bank for Rheumatic Diseases patients (n = 12,215).

Variables	Values
Age, yrs	59.1 (13.3)
Sex, female, %	83.8
College graduate, %	39.7
BMI	29.5 (7.3)
Smoking category, %	
Never	52.8
Past	35.8
Current	11.4
Median household income (US$)	55,000
WPI (0–19)	6.4 (5.6)
SSS (0–12)	4.7 (3.0)
PSD (0–31)	11.0 (7.6)
FM 2016, %	26.4
WSP, %	51.7
Generalized (widespread) pain, %	42.1
VAS pain (0–10)	4.2 (2.8)
PCS (SF-36; 0–100)	36.3 (11.0)
MCS (SF-36; 0–100)	46.9 (12.1)
HAQ-DI (0–3)	1.0 (0.7)
Work disability, %	16.4
EQ-5D (0–1)	0.72 (0.20)
RA, %	73.8
NIRMD, %	26.2

Values are mean (± SD) unless otherwise specified. HAQ-DI: Health Assessment Questionnaire–Disability Index; NIRMD: noninflammatory rheumatic and musculoskeletal disorders; BMI: body mass index; WPI: widespread pain index; SSS: symptom severity score; PSD: polysymptomatic distress scale; FM 2016: 2016 modified American College of Rheumatology criteria for fibromyalgia; WSP: widespread pain; VAS: visual analog scale; PCS: physical component score; MCS: mental component score; SF-36: Medical Outcomes Study Short Form-36; RA: rheumatoid arthritis.

Functional status was measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI)[23]. Quality of life was measured using the EQ-5D[24]. Patients self-reported work disability status. We also obtained patient's reported disability status through US government Social Security pension records. But Social Security disability does not apply after age 65. Therefore, we chose to use the self-report of disability. Results of Social Security disability and self-reported disability in this dataset differ by only 1.4%. VAS pain measures pain intensity while WPI measures the extent of pain sites involved. The measures are different, but are correlated at 0.521 in NDB databases of our study.

Statistical methods. Using observational data, we hypothesized a model in which the presence of comorbid conditions led to increases in FM-related variables as well as in prevalence of FM (Table 2 and Table 3). To test the extent to which individual comorbid conditions were associated with increases in the prevalence of FM&WSP and in WPI, SSS, and PSD scores, we used a treatment effects model that considered each comorbid condition as a treatment (Table 3). A treatment effect is the average effect of a binary (0–1) variable on an outcome variable. The model (Stata's teffects nearest neighbor matching procedure)[25] used 1:4 nearest neighbor matching on age, sex, total household income, BMI, smoking status (never, past, current), and hypertension (HTN). For WPI, SSS, and PSD, results presented are the estimated average comorbidity effect. For FM diagnosis, the average comorbidity effect is the estimated increase in percent FM diagnosis. Similar analyses were performed for the summed categorical comorbidity scores (Table 2), using a regression adjustment (ra) treatment effects model (Stata's teffects ra). Analysis after teffects nearest neighbor matching demonstrated

Table 2. The average effect of individual comorbidity on fibromyalgia (FM) and FM-related variables in 12,215 patients.

Comorbidity	Comorbidity Prevalence (%)	PSD Average Comorbidity Effect	WPI Average Comorbidity Effect	SSS Average Comorbidity Effect	FM Average Comorbidity Effect	FM %, Comorbidity (+) vs Comorbidity (–)
Psychological	24.7	5.0 (4.6–5.3)	2.4 (2.2–2.7)	2.5 (2.4–2.6)	23.3 (21.0–25.6)	46.3 vs 20.2
Neurologic	2.9	4.2 (3.3–5.2)	2.5 (1.7–3.2)	1.8 (1.4–2.1)	18.0 (12.1–23.8)	43.8 vs 25.8
Stroke	0.7	4.0 (1.5–6.5)	3.3 (0.5–4.1)	1.7 (0.7–2.6)	20.0 (6.9–33.1)	46.2 vs 26.2
GI	19.3	3.3 (3.0–3.7)	2.0 (1.7–2.2)	1.4 (1.2–1.5)	14.2 (11.9–16.4)	37.4 vs 23.2
GI (w/o IBS)*	11.0	2.8 (2.3–3.2)	1.6 (1.2–1.9)	1.1 (1.0–1.4)	10.4 (7.3–13.4)	30.1 vs 19.8
Pulmonary	15.3	2.9 (2.4–3.3)	1.8 (1.5–2.1)	1.0 (0.9–1.2)	11.9 (9.4–14.4)	36.3 vs 24.4
Renal	3.5	2.8 (2.0–3.7)	1.6 (0.9–2.2)	1.3 (0.9–1.6)	11.7 (6.0–17.3)	37.7 vs 26.0
Fracture	2.2	2.6 (1.4–3.9)	1.5 (0.7–2.4)	1.1 (0.6–1.5)	12.1 (5.4–18.8)	38.2 vs 26.1
Heart disease	7.8	2.3 (1.8–2.8)	1.3 (0.9–1.7)	1.0 (0.8–1.2)	10.3 (6.8–13.8)	35.7 vs 25.4
Cancer	2.3	2.1 (1.1–3.1)	1.2 (0.4–2.0)	0.9 (0.5–1.3)	13.5 (6.6–20.5)	39.6 vs 26.1
Cataract	9.5	1.8 (1.2–2.4)	1.0 (0.6–1.5)	0.7 (0.5–1.0)	7.5 (4.0–10.9)	33.2 vs 25.7
GU	3.4	1.8 (0.9–2.7)	1.0 (0.3–1.7)	0.8 (0.5–1.9)	6.0 (0.03–12.0)	32.1 vs 26.1
Diabetes	12.0	1.4 (0.9–2.0)	0.8 (0.4–1.2)	0.6 (0.4–0.8)	5.6 (2.1–9.0)	31.3 vs 25.7

Data are % (95% CI) unless otherwise indicated. * n = 9334. Analyses of each comorbidity are nearest neighbor matched 1:4 (comorbid condition: not comorbid condition) on age, sex, total household income, body mass index, smoking status (never, past, current), and hypertension. PSD: polysymptomatic distress scale; WPI: widespread pain index; SSS: symptom severity scale; GI: gastrointestinal; IBS: irritable bowel syndrome; GU: genitourinary.

Table 3. The average effect of multiple comorbidities* on fibromyalgia (FM) and FM-related variables in 12,215 patients.

No. Comorbidities	Comorbidity Prevalence (%)	PSD Average Comorbidity Effect	WPI Average Comorbidity Effect	SSS Average Comorbidity Effect	FM Average Comorbidity Effect	FM %, Comorbidity (+) vs Comorbidity (–)	WSP, Average Comorbidity Effect	WSP %, Comorbidity (+) vs Comorbidity (–)
0	51.7							
≥ 1	48.3	3.0 (2.7–3.3)	1.8 (1.6–2.0)	1.2 (1.1–1.3)	12.2 (10.6–13.8)	32.6 vs 20.4	13.4 (11.5–15.2)	59.2 vs 45.6
1	28.9	2.0 (1.7–2.3)	1.2 (1.0–1.5)	0.8 (0.7–0.9)	7.5 (5.7–9.3)	27.9 vs 20.4	10.5 (8.5–12.6)	56.1 vs 45.6
2	12.5	4.0 (3.6–4.4)	2.4 (2.1–2.7)	1.6 (1.4–1.7)	16.7 (14.0–19.4)	37.1 vs 20.4	16.3 (13.5–19.2)	61.9 vs 45.6
3	4.5	5.8 (5.1–6.5)	3.6 (3.0–4.2)	2.2 (2.0–2.5)	26.4 (21.7–31.2)	46.0 vs 20.4	25.7 (21.0–30.4)	71.3 vs 45.6
4+	2.5	7.8 (6.5–9.0)	4.7 (3.7–5.7)	3.1 (2.7–3.5)	34.9 (27.2–42.6)	55.2 vs 20.4	26.8 (19.7–34.0)	72.4 vs 45.6

* Does not include psychological comorbidity. Data are % (95% CI) unless otherwise indicated. Comorbidities range from 0 to 11. PSD: polysymptomatic distress scale; WPI: widespread pain index; SSS: symptom severity score; WSP: widespread pain.

satisfactory balancing. All results in Table 2 and Table 3 were statistically significant at $p < 0.5$. Graphic figures were based on marginal means obtained following logistic and linear regression analyses using comorbidity variables as dependent variables and covariates cited above as predictor variables.

Ethics. Ethical approval for this study was obtained from the Via Christi Institutional Review Board, Wichita, Kansas, USA (FWA00001005). The study was conducted in accordance with the Declaration of the World Medical Association (www.wma.net) and the Helsinki Declaration of 1975, as revised in 1983. Informed consent from study subjects was obtained as required.

RESULTS

As shown in Table 1, patients in this study had clinically important symptoms and outcomes. WSP was present in 51.7% according to the 1990 ACR definitions[22] and in 42.1% according to 2016 FM criteria. FM was present in 26.4% according to 2016 criteria. Physical impairment was substantial, with a mean SF-36 physical component score of 36.3 and a HAQ functional disability score of 1.0. Work disability was reported in 16.4% of patients. The mean PSD score was 11.0 (7.6), reflecting the contribution of patients with RA [10.6 (7.5)] and patients without [12.2 (7.9)]. Patients with RA constituted 73.8% of the study population and those without RA, 26.2%.

Table 2 describes the relation between 12 individual comorbid conditions and FM-related variables. Of the 12,215 patients in this table, 5252 (43.0%) reported no comorbidities. Table 3 restricts the analyses to 11 aggregated non-psychological disorders. With psychological disorders omitted, 6316 (51.7%) patients reported no comorbid condition. For PSD, WPI, and SSS, we calculated the increase in score, or the average comorbidity effect, conditioned on the presence of the specific comorbidity (Table 2) or on the number of comorbidities (Table 3). For FM, the average comorbidity effect is the percent increase in FM attributable to the comorbidity (Table 2) or level of comorbidity score (Table 3).

Combined comorbidities. As shown in Table 3, patients with at least 1 non-psychological comorbid condition had a PSD, WPI, and SSS increase of 3.0 (95% CI 2.7–3.3), 1.8 (95% CI 1.6–2.0), and 1.2 (95% CI 1.1–1.3) units, respectively, and

an average estimated FM prevalence of 32.6%. The estimated increase in FM and WSP prevalence associated with 1 or more comorbidities was 12.2% (10.6–13.8) and 13.4 (11.5–15.2), respectively. Patients without any comorbid condition had an estimated FM&WSP prevalence 20.4% and 45.6%. As the number of comorbid conditions increased from 1 to 4 or more, PSD, WPI, SSS and the percent with FM increased stepwise. For PSD, the increase associated with 1 and 4 or more comorbidities was 2.0 (95% CI 1.7–2.3) and 7.8 (95% CI 6.5–9.0). For FM the increase was 7.5% (95% CI 5.7–9.3) and 34.9 (95% CI 27.2–42.6); for WSP 10.5 (8.5–12.6) and 26.8 (19.7–34.0).

Individual comorbidities. The relation of individual comorbidities to PSD, WPI, SSS, and FM is shown in Table 2 and Figure 1. The most common individual comorbidity was psychological comorbidity, followed by GI (19.3%), pulmonary (15.3%), and diabetic (12.0%) disorders. Patients reporting psychological comorbidity had the greatest increase in PSD, 5.0 (95% CI 4.6–5.3), and FM, 23.3% (95% CI 21.0–25.6). As shown in column 7 of Table 2, the estimated (potential outcome) percent with FM associated with individual comorbidities ranged from 46.3% and 43.8% for psychological and neurological, respectively, to 32.1% and 31.3% for GU and diabetes, respectively. However, CI around the comorbidity effect could be wide for FM, as in diabetes [5.6 (2.1–9.0)] and cancer [13.5 (6.6–20.5)]. The ranking of comorbidity effect was similar for PSD, WPI, SSS, and FM diagnosis. Because of the potential problem of IBS being both a GI comorbidity and a possible component of FM definition ("pain or cramps in the lower abdomen" in FM 2016 criteria), we also analyzed GI comorbidity after excluding patients with IBS. The exclusion reduced the prevalence of GI comorbidity to 11.0%, the FM average comorbidity effect to 10.4 (95% CI 7.3–13.4), and the PSD increase to 2.8 (95% CI 2.3–3.2) units.

The above analyses examined data from the perspective of a possible causal model that leads from comorbidity to WPI/PSD/FM (i.e., what is the average effect of comorbidity on PSD, WPI, SSS, and FM&WSP). To further understand the relation between comorbidity, WSP, FM, and FM variables, we graphically studied a different perspective in which causation [of cardiovascular (CV) disease] flows from WPI/PSD/FM to comorbidity, or at least, is neutral as to causality. Figure 2 shows that the number of pain sites (Figure 2a and Figure 2b) and the PSD score (Figure 2c and Figure 2d) are associated with increasing probability of

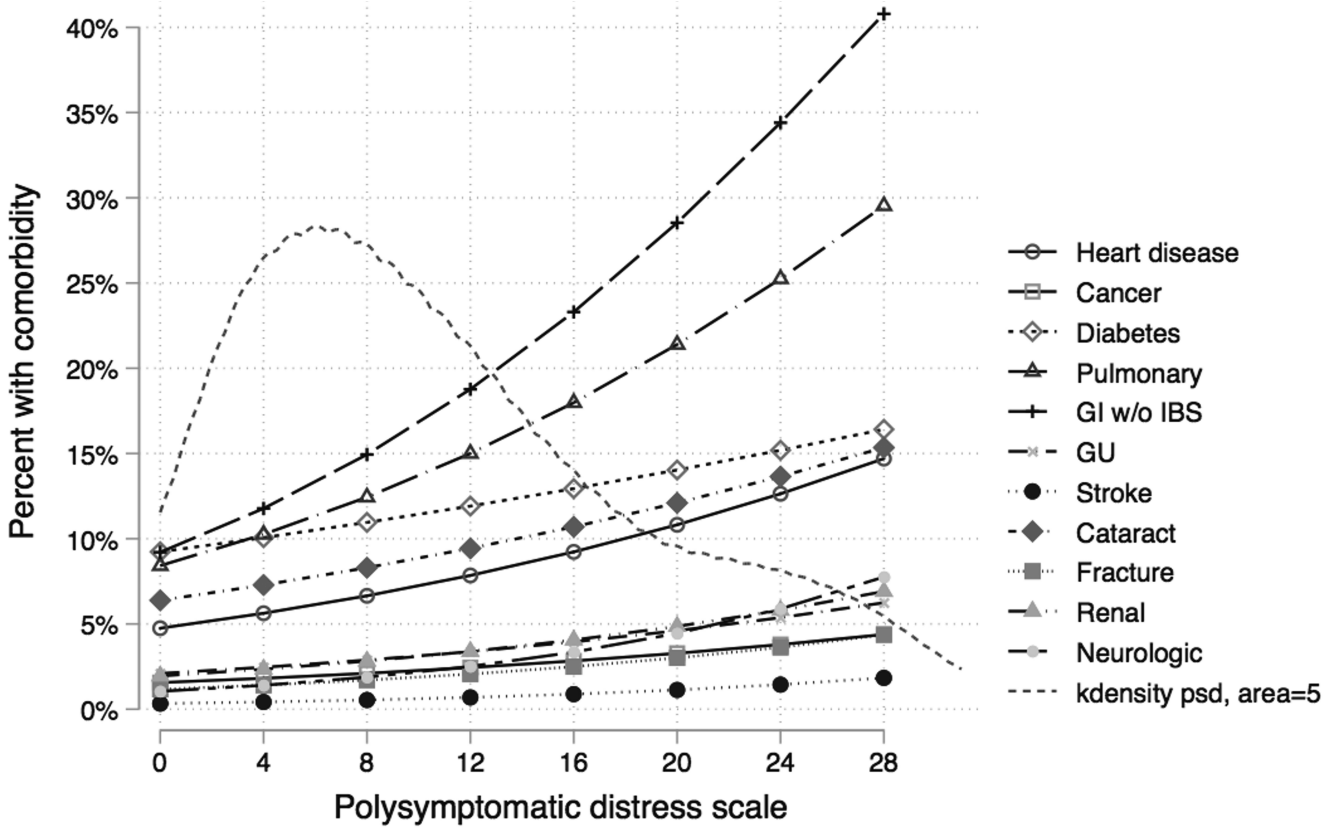

Figure 1. The marginal probability of individual study comorbidities with polysymptomatic distress scores, adjusted for age, sex, BMI, hypertension, smoking status, and total household income. The mean and median PSD scores are 9.0 and 11.0. The PSD density estimate curve is superimposed on the figure. Psychological comorbidity is omitted from this figure, but can be observed in Table 2. PSD: polysymptomatic distress scale; GI: gastrointestinal; IBS: irritable bowel syndrome; GU: genitourinary; kdensity: kernel density estimation; BMI: body mass index.

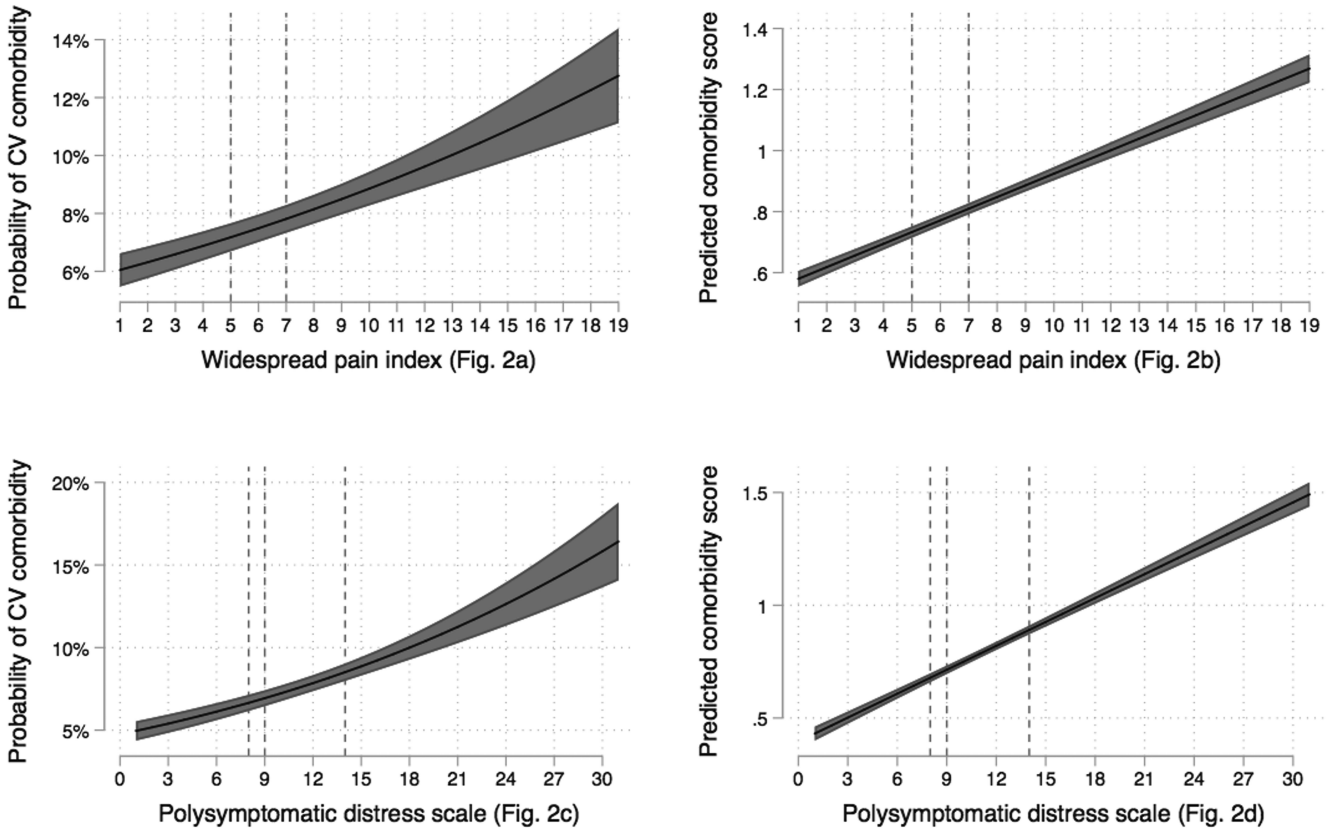

Figure 2. The predicted probability of cardiovascular (CV) comorbidity as a function of the widespread pain index (WPI) and polysymptomatic distress scales (PSD; Figure 2a and Figure 2c). The increase in predicted comorbidity score associated with a 1-unit change in WPI (Figure 2b) and PSD (Figure 2d). The left vertical line is at 10th percentile (5.0) of the WPI distribution in patients with ACR 1990 widespread pain (WSP) and 2016 generalized pain (GP). The right vertical line is the 10th percentile of the PSD in patients satisfying the 2016 fibromyalgia criteria (FM 2016). For Figures 2c and 2d, the left (8.0), center (9.0), and right (14.0) vertical lines for PSD are at the 10th percentile of WSP, GP, and FM 2016–positive patients, respectively. The dark area surrounding each solid line is the 95% CI. ACR: American College of Rheumatology.

reported CV disease and higher (0–11) comorbidity scores. The vertical lines show the lower limits (at the 10th percentile) of WSP and FM. These vertical lines also provide insight into the effect of dichotomizing WPI into WSP classifications and PSD roughly into FM/non-FM. So that our data might be consistent with the CV analyses reported by others and discussed below, we also conducted a covariate-adjusted logistic regression analysis of the effect of FM&WSP on CV comorbidity. The OR for these analyses were 1.8 (95% CI 1.5–20) and 1.5 (95% CI 1.3–1.7), respectively.

DISCUSSION

An important result of our study is to show that it is possible to quantify the relation of comorbidity to FM and FM-related symptoms in definable, reproducible units. The study findings show that comorbidity is associated with increases in all variable scores related to FM, including PSD, WPI, SSS, as well as to FM and WSP diagnoses. These increases occur with each individual comorbidity and increase stepwise with each additional condition. As shown in Figure 1 and Figure 2, the probability of comorbidity increases as PSD and WPI scores increase. That is, the association with comorbidity occurs over the full range of PSD, WPI, and SSS in those satisfying as well as those not satisfying FM (or WSP) criteria.

Previous studies of FM&WSP have been of uniformly high quality, i.e., large and appropriately constituted and analyzed. They include health insurance and health database studies[3,4,5,6] and well-designed epidemiological studies[7,8]. Some studies have been prospective, that is, finding persons who have the baseline condition (presence or absence of WSP or FM) and reassessing them at future times[3,4,7,8], and some are cross-sectional, including the current study and others[5,6].

Tsai, *et al* studied Taiwanese patients treated for FM at least once a month for 3 consecutive months[3]. They found that patients with FM showed a significantly higher risk of a coronary heart disease event (HR 2.1, 95% CI 1.5–3.1) than did patients without FM. Patients with FM in their study also had a greater prevalence of HTN, diabetes, and chronic obstructive pulmonary diseases than non-FM patients. A second health insurance database from Taiwan found an adjusted HR for coronary heart disease in patients with FM (relative to reference subjects) of 1.5 (95% CI 1.4–1.5)[4]. That

study also found evidence of increased prevalence of diabetes, HTN, and cerebrovascular disease. In an Israeli health services database, the OR for the associations of FM with diabetes was 1.2 (95% CI 1.1–1.2)[5].

Epidemiological studies from the UK involving patients with WSP have shown increased risks of mortality from cancer[7,8] and CV disease[8], and the mortality risk from both cancer and CV deaths was found to increase as the number of pain sites that subjects reported increased[8]. Using the 2012 US National Health Interview Survey and a surrogate definition of FM modeled on the PSD scale, Walitt, *et al* found associations between FM and almost all major medical conditions, and showed that persons with more symptoms were more likely to have comorbid conditions[6].

Our study adds important information to what is known about FM&WSP and comorbidity. First, we confirm the above published reports regarding CV disease, diabetes, and cancer, but, in agreement with Walitt, *et al*[6], extend the observations to include all physical comorbidities studied (i.e., neurological, stroke, GI, pulmonary, renal, fractures, cataract, and genitourinary disorders). Second, we provide quantitative measurements of the relation of comorbid conditions to FM-related variables. For example, the presence of 1 comorbid condition (compared with none) is associated with an increase in the PSD of 2 units, WPI of 1.8 units, FM of 7.5%, and WSP of 8.6%. Additionally, and perhaps more importantly, the demonstration that severity of symptoms or extent of pain is a more important determinant of comorbidity association than categories of FM or WSP is a central finding, and is in agreement with the suggestions of others[3,4,8]. The strength PSD and WPI associations with comorbidities are independent of the distributions of PSD and WPI, but associations of FM&WSP can be dependent on PSD and WPI distributions because they rely on cutpoints in those distributions (Figure 1 and Figure 2). It should be recognized that the range of PSD and WPI values in FM- or WSP-positive patients is large, so the risk of comorbidities depends on patients' severity within the FM or WSP group. However, categorization into WSP and FM effectively treats all patients as if they were the same.

The mechanism by which comorbidity and FM-related variables covary is unclear and uncertain. McBeth, *et al*, in 2003[7] wrote that there was no convincing explanation for their observation linking WSP and cancer. Causality of pain or FM&WSP and comorbidity is complex. The statistical models of the studies cited above are predictive rather than causal[26]. For example, logistic regression of FM on CVD adjusted for age and sex in our current study yields an OR of 2.1 (95% CI 1.8–2.3), while the reversed model (CVD on FM) has an OR of 2.1 (95% CI 1.8–2.4). A causal model by contrast posits a direction, such as that there is a causal path from FM&WSP to comorbidity or the reverse. The most important reason for the failure of causal models is omitted variables, variables "that both affect the dependent variable and are correlated with the variables that are currently in the model. Omission of such variables can totally invalidate [study] conclusions" (Allison)[26]. FM&WSP associations include complex physical and mental stressors, and psychosocial and central factors, including interactions that we can hypothesize about, but are unmeasurable. An additional issue in causal inference is multicollinearity, because it can be very difficult to get reliable estimates of 1 covariate while controlling for the others, as for example, WPI and SSS together, or trying to understand the importance of symptom variables in the presence of WSP and PSD.

To add further to the complexity of causality related to FM&WSP variables, we suggest that the associations noted are not unique to WSP and FM. A 2019 study reported that persons with RA can have many comorbidities[27]. Von Korff, *et al* found "… that chronic spinal pain is typically comorbid with … chronic physical diseases. … we have no ready explanations why chronic spinal pain was comorbid with some [physical diseases] and not others[28]." These observations tally with the observations that the number of pain sites, even below the requirements for WSP and FM, correlate with comorbidity.

How can we explain the findings of our study and those cited above? A common view, to which we subscribe, as expressed by Cohen and Quintner, is that "FM reflects a distressed organism where the sources of distress may be multiple[17]." Although the causal paths between comorbid conditions and FM are complex and not easily discernible[13,29,30], we believe that there is substantial evidence to implicate stress as a key causal factor[31,32,33,34]. Stress-related antecedents of FM for which there is substantial evidence include life stresses, such as early life trauma, traumatic and posttraumatic stresses, depression[35,36], and major life stresses such as life-threatening and emotional abuse, and physical and sexual trauma[37]. From the perspective of comorbidity, each of the comorbid events of this study might be considered a stressor representing a signal or intimation of disability, loss of income and control, and of mortality.

Limitations. Both self-reported data and International Classification of Diseases data have some acknowledged problems with validity and reliability[38,39,40,41]. However, there is no identifiable pattern of bias that could explain the consistent association of pain with comorbidity in the current study and other studies cited. It is possible that differential misclassification through patient overreporting might have inflated the association between FM and comorbidity. But simulation studies (data not shown) suggest this effect, if present, would have been small.

The inability to deal with omitted observed and latent variables is a limitation of all studies and an acknowledgment of the complexity of the interaction between comorbidity, FM, and stressors. Another limitation of our study was its cross-sectional nature. Although the NDB has longitudinal data, the required granularity of assessments of comorbidity

onset and FM timing and the requirement for incident cases precluded our using such analytic methods. Another potential limitation is our combined use of 9017 patients with RA, an inflammatory disorder, and 3198 with NIRMD, because it is possible that persons with RA might have different levels of comorbidity. However, we have recently shown that FM characteristics are the same in "primary" and "secondary" FM[20]. Although we did not report on comorbidity scores in that report, data from that study showed that when adjusted for age, sex, and PSD, there was no statistically significant difference in comorbidity scores for RA versus non-RA patients.

We have shown that for all comorbid conditions studied, comorbidity is associated with increases in FM&WSP prevalence and in continuous measures of FM-related variables. FM and FMV are associated with increase in the number of comorbidities, and the association can be measured quantitatively. However, the association with WSP and FM may be an effect of definitions of those conditions, because comorbidity increases are also present with subsyndromal levels of WSP and FM.

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