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The relation of physical comorbidity and multimorbidity to fibromyalgia, widespread pain and fibromyalgia-related variables

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Abstract

Objective. To investigate the relation of physical (non-psychological) comorbidity and multimorbidity to quantitative measures of fibromyalgia and musculoskeletal pain.
Methods. We studied 12, 215 patients in a research databank with quantitative measures of fibromyalgia related variables (FMV) that included binary determinations of fibromyalgia and widespread pain, and constituent variables of fibromyalgia diagnosis that included the widespread pain index (WPI), symptom severity score (SSS) and the polysymptomatic distress scale (PSD). We assessed 10 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, 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 fibromyalgia percent increased stepwise. For patients with ≥4 conditions, the predicted prevalence of fibromyalgia was 55.2%.
Conclusion. Fibromyalgia and FMV are associated with increase in the number of comorbidities, and the association can be measured quantitatively. However, the association with widespread pain and fibromyalgia may be an effect of man-made definitions of widespread pain and fibromyalgia, as comorbidity increases are also present with sub-syndromal levels of widespread pain and fibromyalgia.

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Importance

It is possible to quantify the relation of comorbidity to fibromyalgia and fibromyalgia-related symptoms in definable, reproducible units: PSD, WPI, fibromyalgia.

The presence of comorbidity is associated with increases in all variable scores related to fibromyalgia, including PSD, WPI, SSS and fibromyalgia. This observation is seen for comorbid conditions overall, as well as for each individual comorbid condition.

The more comorbid conditions present, the greater the PSD, WPI, SSS scores and fibromyalgia prevalence.

Unlike diagnosis independent levels of PSD, WPI, SSS, study and population-based odds ratio estimates of the association of widespread pain and fibromyalgia are dependent on definitions of widespread pain and fibromyalgia and the distribution of PSD in the population.

The association of comorbidity with widespread pain and fibromyalgia may be an effect of the man-made definitions of widespread pain and fibromyalgia, as comorbidities are associated with sub-syndromal levels of widespread pain and fibromyalgia.

Among the observed characteristics of fibromyalgia and widespread pain (FM&WSP) is their association with psychological (1, 2) and physical (non-psychological) comorbid disorders (3-8). Psychological disorders are increased in FM&WSP, and the relationship between FM&WSP and psychological disorders is generally understood to be bidirectional with respect to causation (9-11).

Physical comorbid conditions are less well characterized, as 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 (12)," the mechanisms by which cancer or neurological disorders, for example, are associated with FM&PSD remain unknown (7). Recent interest in complex systems and network models may offer future insights into FM&WSP issues (13, 14).

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

One idea relating to the causation of fibromyalgia is that it "reflects a distressed organism where the sources of distress may be multiple" (17). We hypothesize that one such stressor is comorbid disease. We examine the data from the causal perspective that comorbid disease influences the risk of fibromyalgia and change in FMV. From these data, we measure the risk of fibromyalgia 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.

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 fibromyalgia diagnosis and fibromyalgia related variables. Data from semiannual self-report questionnaires were collected from 2009, the time that fibromyalgia criteria variables first became available in the NDB, through 2014. As patients may have had multiple 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 this study, we identified 2 diagnostic groups of patients with pain, 9,017 patients with rheumatoid arthritis (RA) and 3,198 referred with noninflammatory rheumatic and musculoskeletal disorders (NIRMD), including fibromyalgia, 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 fibromyalgia are effectively the same with respect to diagnosis and outcomes (20).

Outcome variables. The outcome variables were a) fibromyalgia diagnosis by 2016 modified American College of Rheumatology (ACR) criteria (16), and 3 component variables of the 2016 criteria: b) the widespread pain index (WPI), c) the symptom severity scale (SSS), and d) the polysymptomatic distress (PSD) scale). 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 Symptom severity scale (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 been bothered by that occurred during the previous 6 months: (1) headaches (0–1), (2) pain or cramps in lower abdomen (0–1) and (3) depression (0–1). The polysymptomatic distress scale (0-31) is the sum of the WPI and SSS. The PSD measures the magnitude and severity of fibromyalgia symptoms in those satisfying and not satisfying criteria. By definition, fibromyalgia criteria cannot be satisfied if the PSD is <12. We identified widespread pain (WSP) using the definition of the 1990 fibromyalgia criteria (22) as "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 widespread pain definition of the 2016 fibromyalgia 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 this "problem 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) Uterus, ovaries, etc. (women) 9) Renal: Kidney problem; 10) Cancer; 11) Neurological: Neurological problem (like 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."

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), fibromyalgia diagnosis, WPI, SSS, PSD, widespread pain, visual analog score (VAS) pain, the physical and mental component of the short form-36 (SF-36). Functional status was measured using the Health Assessment Question-Disability Index (HAQ) (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 by US government social security pension. 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 extent of pain sites involved. The measures are different, but are correlated at 0.521 in NDB databases of this study.

Statistical methods. Using observational data, we hypothesized a model in which the presence of comorbid conditions led to increases in fibromyalgia-related variables as well as in prevalence of

fibromyalgia (Tables 2 and 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 utilized 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 nnm* procedure)(25) utilized 1:4 nearest neighbor matching on age, sex, total household income, BMI, smoking status (never, past, current) and hypertension. 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 treatment effects model (Stata's teffects ra). Analysis after *teeffects nnm* demonstrated satisfactory balancing. All results in Tables 2 and 3 were statistically significant at $p<0.5$. Graphic figures were based on marginal means obtained following logistic and linear regression analyses utilizing comorbidity variables as dependent variables and covariates cited above as predictor variables.

Ethics. Ethical approval for this study was obtained from the Via Christi IRB, 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. 51.9% had widespread pain according to the 1990 ACR definitions (22) and 42.1% according to 2016 fibromyalgia criteria. Fibromyalgia 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 1.0. Work disability was reported in 16.4% of patients. The mean PSD score was 11.0 (7.6), reflecting the contribution of RA 10.6 (7.5) and non-RA patients, 12.2 (7.9). RA patients constituted 73.8% of the study population and non-RA constituted 26.2%.

Table 2 describes the relationship between 12 individual comorbid conditions and fibromyalgia related variables. Of the 12, 215 patients in this table, 5,252 (43.0%) reported no comorbidities. Table 3 restricts the analyses to 11 aggregated non-psychological disorders. With psychological disorders omitted, 6,316 (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 fibromyalgia, the average comorbidity effect is the percent increase in fibromyalgia 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, and an average estimated fibromyalgia prevalence 32.6%. The estimated increase in fibromyalgia and WSP prevalence associated with 1 or more comorbidities was 12.2% (10.6-13.8) and 13.4 (11.5-15.2). Patients without any comorbid condition had an

estimated fibromyalgia and 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 fibromyalgia 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 fibromyalgia 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 relationship of individual comorbidities to PSD, WPI, SSS and fibromyalgia is shown in Table 2 and Figure 1. The most common individual comorbidity was psychological comorbidity, followed by gastrointestinal (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 fibromyalgia, 23.3% (95% CI 21.0-25.6). As shown in column 7 (last column) the estimated (potential outcome) percent with fibromyalgia associated with individual comorbidities ranged from 46.3% and 43.8% for psychological and neurological to 32.1% and 31.3% for GU and diabetes. However, confidence intervals around the comorbidity effect could be wide for fibromyalgia, 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 fibromyalgia diagnosis. Because of the potential problem of irritable bowel syndrome (IBS) being a both a GI comorbidity and a possible component of fibromyalgia definition ("pain or cramps in the lower abdomen" in fibromyalgia 2016 criteria), we also analyzed GI comorbidity after excluding patients with IBS. The exclusion reduced the prevalence of GI comorbidity to 11.0%, the fibromyalgia 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/Fibromyalgia; i.e., what is the average effect of comorbidity on PSD, WPI, SSS and FM&WSP. To further understand the relation between comorbidity, widespread pain, fibromyalgia and fibromyalgia variables, we graphically studied a different perspective in which causation (of cardiovascular disease) flows from WPI/PSD/Fibromyalgia to comorbidity or, at least, is neutral as to causality. Figure 2 shows that the number of pain sites (Fig. 2a and 2b) and the PSD score (Fig 2c and Fig. 2d) are associated with increasing probability of reported cardiovascular disease and higher (0-11) comorbidity scores. The vertical lines show the lower limits (at the 10^{th} percentile) of widespread pain and fibromyalgia. These vertical lines also provide insight into the effect of dichotomizing WPI into widespread pain classifications and PSD roughly into fibromyalgia/non-fibromyalgia. So that our data might be consistent with the cardiovascular analyses reported by others and discussed below, we also conducted a covariate adjusted logistic regression analysis of effect of fibromyalgia and widespread pain on cardiovascular comorbidity. The odds ratios 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 this study is to show that it is possible to quantify the relation of comorbidity to fibromyalgia and fibromyalgia-related symptoms in definable, reproducible units. The study findings show that comorbidity is associated with increases in all variable scores related to fibromyalgia, including PSD, WPI, SSS, as well as to fibromyalgia and widespread pain diagnosis

itself. These increases occur with each individual comorbidity and increase step-wise with each additional condition. As shown in Fig. 1 and Fig. 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 fibromyalgia (or widespread pain) criteria.

Previous studies of FM&WSP have been of uniformly high quality—large, appropriately constituted and analyzed. They include health insurance and health database studies (3-6) 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 widespread pain or fibromyalgia) and reassessing them at future times (3, 4, 7, 8), and some are cross-sectional, including the current study and others (5, 6).

Tsai studied Taiwanese patients treated for fibromyalgia at least once a month for 3 consecutive months (3). "Patients with fibromyalgia showed a significantly higher subsequent risk of a coronary heart disease event (hazard ratio, 2.1 (95% CI 1.5–3.1) than patients without fibromyalgia." Fibromyalgia patients in their study also had a greater prevalence of hypertension, diabetes and chronic obstructive pulmonary diseases than non-fibromyalgia patients. A 2nd health insurance database from Taiwan found an adjusted hazard ratio for "coronary heart disease" in fibromyalgia patients relative to reference subjects" of 1.5 (95% CI 1.4-1.5) (4). They also found evidence of increased prevalence of diabetes, hypertension and cerebrovascular disease. In an Israeli health services database, the odds ratio for the associations of fibromyalgia with diabetes was 1.2 (95% CI 1.1–1.2)(5) .

Epidemiological studies from the UK, involving patients with widespread pain, have shown increased risks of mortality from cancer (7, 8) and cardiovascular disease (8), and the mortality risk from both cancer and cardiovascular 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 fibromyalgia modeled on the PSD scale, Walitt found associations between fibromyalgia 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 with respect to cardiovascular disease, diabetes and cancer, but, in agreement with Walitt (6), extend the observations to include all physical comorbidities studied, including neurological, stroke, gastrointestinal, pulmonary, renal, fractures, cataract and genitourinary disorders. Second, we provide quantitative measurements of the relation of comorbid conditions to fibromyalgia 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, fibromyalgia 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 fibromyalgia or WSP is a central finding, and is in agreement with 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 and WSP can be dependent on PSD and WPI distributions because they rely on cut points in those distributions (See Figs. 1 and 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 fibromyalgia effectively treat all patients as if they were the same.

The mechanism by which comorbidity and fibromyalgia-related variables covary is unclear and uncertain. McBeth, in 2003 (7), wrote that there was "no convincing explanation" for their observation linking widespread pain 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 models (26). For example, logistic regression of fibromyalgia on CVD adjusted for age and sex in the current study yields an odds ratio of 2.1 (95% CI 1.8-2.3), while the reversed model (CVD on fibromyalgia) has an odds ratio of 2.1 (95% CI 1.8-2.4). A causal model, by contrast posits a direction, such as 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 (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, as it can be very difficult to get reliable estimates of one 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 fibromyalgia. A 2019 study reported that persons with rheumatoid arthritis "present with numerous comorbidities" (27). Von Korff 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 fibromyalgia, correlate with comorbidity.

How can we explain the findings of our study and those cited above? A common view, to which we subscribe, is that "fibromyalgia reflects a distressed organism where the sources of distress may be multiple (17)." Although the causal paths between comorbid conditions and fibromyalgia are complex and not easily discernible (13, 29, 30), we believe that there is substantial evidence to implicate stress as a key causal factor (31-34). Stress-related antecedents of fibromyalgia for which there is substantial evidence include life stresses, including early life trauma, traumatic and post-traumatic stresses, depression (35, 36); and major life stresses including 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 ICD data have some acknowledged problems with validity and reliability (38-41). 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 by virtue of fibromyalgia patient over-reporting might have inflated the association between fibromyalgia 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, fibromyalgia 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 fibromyalgia timing and the requirement for incident cases precluded our using such analytic methods. Another potential limitation is our combined use of 9,017 patients with rheumatoid arthritis, an inflammatory disorder and 3,198 with noninflammatory rheumatic and musculoskeletal disorders, as it is possible persons with RA might have different levels of comorbidity. However, we have recently shown that fibromyalgia characteristics are the same in "primary" and "secondary" fibromyalgia (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 vs. non-RA patients.

In summary, we have shown that for all comorbid conditions studied, comorbidity is associated with increases in fibromyalgia and widespread pain prevalence and in continuous measures of fibromyalgia 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 man-made definitions of WSP and FM, as comorbidity increases are also present with sub-syndromal levels of widespread pain and fibromyalgia.

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

Variables	Mean or %
N	N=12,215
Age (years)	59.1 (13.3)
Sex (%)	83.8
College graduate (%)	39.7
Body mass index	29.5 (7.3)
Smoking category	
Never (%)	52.8
Past (%)	35.8
Current (%)	11.4
Median household income ($)	55,000
Widespread pain index (0-19)	6.4 (5.6)
Symptom severity score (SSS) (0-12)	4.7 (3.0)
Polysymptomatic distress scale (PSD) (0-31)	11.0 (7.6)
FM 2016 (%)	26.4
Widespread pain (%)	51.7
Generalized (Widespread) pain (%)	42.1
VAS pain (0-10)	4.2 (2.8)
Physical component score (SF-36) (0-100)	36.3 (11.0)
Mental component score (SF-36) (0-100)	46.9 (12.1)
Health assessment questionnaire (HAQ) disability index (0-3)	1.0 (0.7)
Work disability (%)	16.4
EuroQol (0-1)	0.72 (0.20)
Rheumatoid arthritis (RA) (%)	73.8
Non-inflammatory rheumatic and musculoskeletal diseases (NIRMD) (%)	26.2

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

Comorbidity	Comorbidity Prevalence (%)	PSD Average comorbidity effect (95% C.I.)	WPI Average comorbidity effect (95% C.I.)	SSS Average comorbidity effect (95% C.I.)	Fibromyalgia Average comorbidity effect % (95% C.I.)	Fibromyalgia % 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

*N=9,334. PSD=polysymptomatic distress; WPI=widespread pain index; SSS symptom severity scale; GI=gastrointestinal; GU=genitourinary;=irritable bowel syndrome. Analysis of each comorbidity are nearest neighbor matched 1:4 (comorbid condition: not comorbid condition) on age, sex, total household income, BMI, smoking status (never, past, current) and hypertension.

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

Comorbidity	Comorbidity Prevalence (%)	PSD Average comorbidity effect (95% C.I.)	WPI Average comorbidity effect (95% C.I.)	SSS Average comorbidity effect (95% C.I.)	Fibromyalgia Average comorbidity effect % (95% C.I.)	Fibromyalgia % Comorbidity (+) vs. Comorbidity (-)
0 comorbidities	51.7					
≥1 comorbidity	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
1 comorbidity	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
2 comorbidities	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
3 comorbidities	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
4+ comorbidities	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

Comorbidity	Comorbidity Prevalence (%)	WSP % Average comorbidity effect % (95% C.I.)	WSP % Comorbidity (+) vs. Comorbidity (-)
0 comorbidities	51.7		
≥1 comorbidity	48.3	13.4 (11.5-15.2)	59.2 vs. 45.6
1 comorbidity	28.9	10.5 (8.5-12.6)	56.1 vs. 45.6
2 comorbidities	12.5	16.3 (13.5-19.2)	61.9 vs. 45.6
3 comorbidities	4.5	25.7 (21.0-30.4)	71.3 vs. 45.6
4+ comorbidities	2.5	26.8 (19.7-34.0)	72.4 vs. 45.6

Does not include psychological comorbidity. Comorbidities range from 0 to 11.

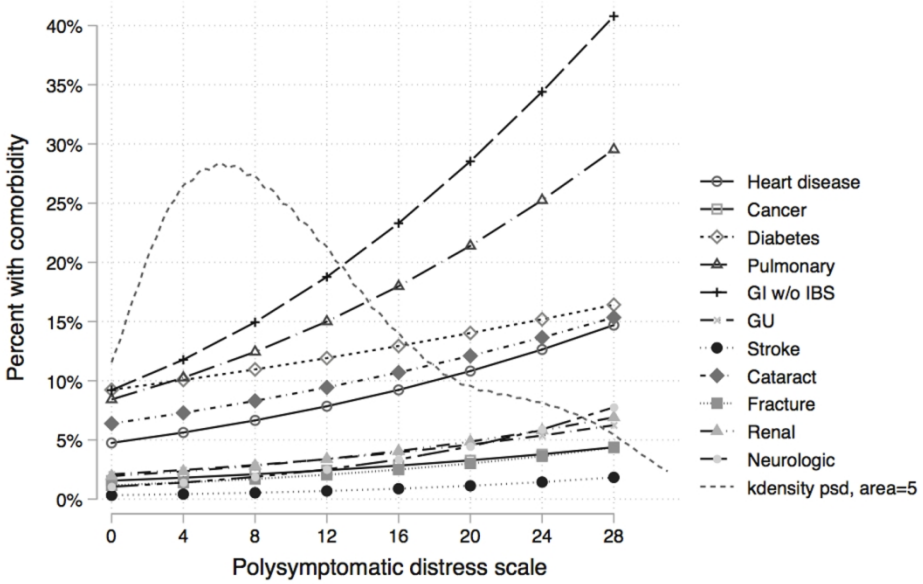

Figure 1. The marginal probability of individual study comorbidities with polysymptomatic distress scores, adjusted for age, sex, body mass index (BMI), hypertension, smoking status and total household income. The mean and median PSD scores are 9.0 and 11.0. The PSD density estimate curve is superimposed on the figures. Psychological comorbidity is omitted from this figure, but can be observed in Table 2.

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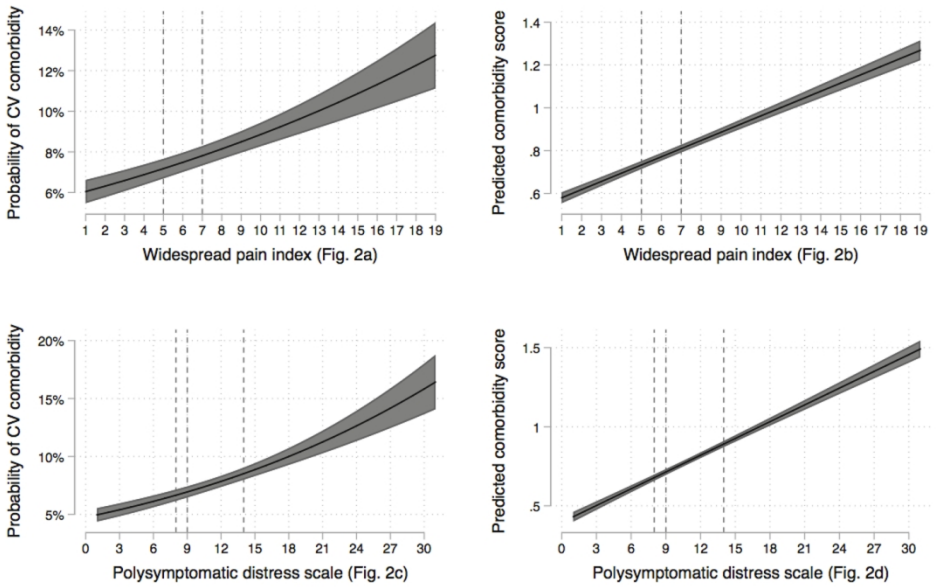

Figure 2. The predicted probability of CV comorbidity as a function of the widespread pain index (WPI) and polysymptomatic distress scales (PSD) (Fig 2a and Fig 2c). The increase in predicted comorbidity score associated with a 1-unit change in WPI (Fig. 2b) and PSD (Fig. 2d) The left vertical line is at 10th percentile (5.0) of the WPI distribution in patients with ACR 1990 widespread pain (WSP) and 2016 generalized pain (GP), the right line at the 10th percentile of the PSD in patients satisfying 2016 fibromyalgia criteria (FM2016). For Figs. 2c and 2d, the left (8.0), center (9.0) and right (14.0) vertical lines PSD are at the 10th percentile of WSP, GP, and FM2016 positive patients. Black area surrounding each solid like is the 95% CI.

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