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All-cause and cause-specific mortality in persons with fibromyalgia and widespread pain: An observational study in 35,248 persons with rheumatoid arthritis, non-inflammatory rheumatic disorders and clinical fibromyalgia

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ABSTRACT

Purpose: Studies of the relation of fibromyalgia (FM) and widespread pain (WSP) to mortality have differed as to the presence or absence of an association and the extent of cause-specific mortality. However, no studies have investigated which definitions of FM and WSP associate with mortality, nor of FM mortality in other diseases. We investigated these issues and the meaning of mortality in patients with FM.
Methods: We used Cox regression to study 35,248 rheumatic disease patients with up to 16 years of mortality follow-up in all patients and separately in those with diagnoses of rheumatoid arthritis (RA) (*N* = 26,458), non-inflammatory rheumatic disorders (NIRMD) (*N* = 5,167) and clinically diagnosed FM (*N* = 3,659). We applied 2016 FM criteria and other FM and WSP criteria to models adjusted for age and sex as well as to models that included a full range of covariates, including comorbid disease and functional status. We estimated the degree of explained of variance (R2) as a measure of predictive ability.
Results: We found positive associations between al'l definitions of FM and WSP and all-cause mortality, with relative risks (RR)s ranging from 1.19 (95%CI 1.15–1.24) for American College of Rheumatology (ACR) 1990 WSP to 1.38 (1.31–1.46) in age and sex adjusted revised 2016 criteria (FM 2016). However, in full covariate models the FM 2016 RR reduced further to 1.15 (1.09–1.22). The association with mortality was noted with RA (1.52 (1.43–1.61)), NIRMD (1.43 (1.24–1.66)) and clinical FM (1.41 (1.14–1.75) - where 37% of FM diagnosed patients did not satisfy FM 2016 criteria. In the all-patient analyses, the age and sex explained variation (R2) was 0.255, increasing to 0.264 (4.4%) when FM 2016 criteria were added, and to 0.378 in a full covariate model. Death causes related to FM 2016 status included accidents, 1.45 (1.11–1.91); diabetes 1.78 (1.16–2,71); suicide, 3.01 (1.55–5.84) and hypertensive related disorders, 3.01 (1.55–5.84). Cancer deaths were less common 0.77 (0.68–0.88).
Conclusions: FM is weakly associated with mortality within all criteria definitions of FM and WSP examined (3.4% of explained variance), and across all diseases (RA, NIRMD, clinical FM) equally. Clinical and criteria-defined FM had different mortality outcomes. We found no evidence for a positive association of cancer and FM or WSP.

Abbreviations: ACR, American College of Rheumatology; CWP, chronic widespread pain; FM, fibromyalgia; HAQ, Health assessment questionnaire; IRB, institutional review board; MRR, mortality risk ratio; NDB, National Data Bank for Rheumatic Diseases; NIRMD, non-inflammatory rheumatic disorders; OA, osteoarthritis; OR, odds ratio; PSD, polysymptomatic distress; R2, explained variance; RA, rheumatoid arthritis; RR, relative risk; SMR, standardized mortality ratio; SSS, symptom severity scale; WPI, widespread pain index; WSP, widespread pain

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Introduction

Chronic widespread pain (CWP) occurs in10-12% of the general population [1], and fibromyalgia in 2–4% [2]. There have been two studies of all-cause mortality in persons with fibromyalgia (FM) [3,4] and five studies of chronic WSP (CWP) [5–11]. Both FM studies found no association of FM with mortality, while a meta-analysis of CWP studies reported an all-cause mortality risk ratio (MRR) of 1.22, 95%CI 0.93–1.60. Subsequently, a 2017 study reported an all-cause restricted covariate MRR of 2.43, (95%CI 2.17–2.72) and a cancer MRR of 1.73, (95%CI 1.46–2.05).

In our 2011 report on mortality in patients with a clinical diagnosis of FM (SMR 0.90, 95%CI 0.61–1.26), we concluded that "Mortality does not appear to be increased in patients diagnosed with fibromyalgia ... ." Since the time of that report, however, a number of changes in understanding mortality issues have come to the fore and have led us to reevaluate the mortality question. It is now clear that FM and WSP are associated with extensive co and multi-morbidity that should be expected to result in increased mortality [11–16]. We now know that many patients with a clinical diagnosis of FM do not satisfy FM criteria, and that non criteria-based clinical FM is less severe [17–20]. FM can be identified and diagnosed in patients with rheumatoid arthritis (RA) and osteoarthritis (OA). Reliability problems with the American College of Rheumatology (ACR) 1990 criteria have been noted as well as bias in the identification of FM patients [21,22]. In addition, the standardized mortality ratio (SMR) is problematic and may be severely biased in selected samples, particularly when the distribution of expected deaths over strata [e.g., age] is different in the two comparison cohorts, when case mixes are different, and when there are differences in referral bias and disease severity [23–26]. Finally, even if FM and WSP are associated with mortality, it must be demonstrated that strength of association—the explanatory power of the FM or WSP measure—is sufficient to be used as a marker for increased mortality [27]. Factors such as these were not adequately considered at the time of our original report, and in other studies, and have led us to reexamine the mortality issue while adding five additional years of data and follow-up.

The goals of this current study are several: 1) to determine if FM, including FM in RA and non-inflammatory rheumatic disorders (NIRMD), is associated with increased mortality; 2) to test which FM and WSP criteria best characterize the mortality association; 3) to quantify the strength of the FM and WSP association with measures of explained variation; 4) to understand if the proposed association of FM and WSP with cancer mortality can be substantiated [9]; 5) to apply a continual scale rather than binary diagnostic criteria to FM and mortality; 6) to understand if clinical FM and criteria-based FM are similarly associated with mortality.; and 7) to investigate the role of co and multi-morbidity in the association of FM and mortality.

Methods

Patients

We studied 35, 248 patients with rheumatic diseases between the ages of 21 and 103 years who were referred by rheumatologists to the National Data Bank for Rheumatic Diseases (NDB), a research data bank. Patients complete a detailed questionnaire on a semiannual basis. A comprehensive description of the NDB and its methods has been reported elsewhere [28]. Data for the current study was collected between July 1999 and December 2014, and represents the first (enrollment) questionnaire completed by each patient. The mean time in the study was 9.3 (SD 5.1) years. Every year we queried the National Death Index (NDI) for participant deaths, and we also received death information from relatives of study participants. The NDI collects data from state death certificates and uses this information to provide a primary cause of death. NDI data in the study is complete through December 31, 2015, the date at which the study ends.

Study participants had referral diagnoses of RA, N = 26,458; NIRMD, N = 5167; and FM, N = 3659. Patients with NIRMD had non-inflammatory regional musculoskeletal pain disorder or osteoarthritis. Patients with diagnoses other than RA, NIRMD or FM were excluded. The clinical rheumatic disease diagnoses were made by the patient's rheumatologist or confirmed by the patient's physician in the small number of cases that were self-referred.

Variables

Except for death data, all variables are self-reported. The primary study variables are diagnostic criteria variables. They include criteria: the 2011 (FM 2011) and 2016 modifactions (FM 2016) of the 2010 ACR preliminary diagnostic criteria for FM [29–31]. For the assessment of chronic WSP (CWP) we used 3 variables, the 1990 ACR "4 quadrant pain" (1990 WSP) [32], the 2016 definition from FM 2016 (2016 WSP) [31], and 2019 WSP [33]. The description and details of the WSP criteria are described in detail in a 2019 paper [33]. Briefly, the 1990 criteria loosely identify 4 quadrant pain; the 2016 criteria make certain that at least 4 of 5 body regions have pain; and 2019 criteria require the 2016 definition plus at least 7 sites with pain. To satisfy criteria, symptoms are to be generally present for at least 3 months."

The polysymptomatic distress (PSD) score is the sum of the WSP index (WPI) and Symptom Severity Scale (SSS) of FM 2011 and FM 2016 [29]. The PSD scale 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. PSD severity has also been categorized as 0–3 none, 4–7 mild, 8–11 moderate, 12–19 severe, and 20–31 very severe [34], and is used that way in this study.

Functional disability was measured using the Health Assessment Question-Disability Index (HAQ) [35]. This is a widely used scale that has been shown to be the best predictor of mortality in studies of RA [36,37].

Body mass index was calculated using World Health Organization (WHO) criteria [38].

Comorbidity variables

In a section in the NDB study questionnaire labeled "Current Health Problems," patients were asked to check a box if they had "this problem in the last 6 months." Of the 12 categories available, in this report we studied Diabetes; Pulmonary: lung problems or asthma; Psychological: depression, Renal: kidney problem; Cancer; and Heart: heart attack or other heart problem. A detailed description of these variables in FM is in press (Wolfe, F. et al., "The relation of physical comorbidity and multi morbidity to fibromyalgia, WSP and fibromyalgia-related variables)."

Missing data

There were two type of missing data. Fibromyalgia criteria in this study that had missing data were FM 2011 and FM 2016 criteria. This occurred because the 2011 criteria utilized the SSS and WPI, and SSS was not defined in criteria until 2011, though available in the NDB in 2009. To calculate FM 2011 and FM 2016 criteria for observations prior to 2009, it was necessary to estimate a predicted SSS from variables similar to SSS variables available in the NDB databank prior to 2009, and then combine that with WPI. We did this using the following non-missing variables in a regression analysis to predict SSS: VAS fatigue, VAS sleep disturbance, count of self-reported symptoms, presence or absence of memory problems, age and sex. From the predicted SSS, we calculated predicted values for FM 2011 and FM 2016

by substituting the predicted value of SSS for the missing value. Analysis of agreement between FM 2016 and predicted FM 2016 resulted in 91.6% agreement and a kappa score of 0.827 (almost perfect agreement) [39]. Based on these analyses we combined the 8069 full data for NDB enrollees after 2009 with the 27,215 partially predicted data for enrollees from 1999 through 2009. It should be noted that WPI, which is the strongest predictor of fibromyalgia and the dominent component of the 2016 and 2011 criteria, was never missing. None of the WSP related variables had missing data. In the results section we treat FM 2016 as the primary outcome, but we also present FM 2011 data. Missing data in other study non-criteria variables were few, generally ≤2.5%. In instances when participants had more than one observation in the databank, we substituted the first non-missing value for the missing value. As missing data were few we used simple methods of imputing data, including nearest neighbor matching or mean substitution by sex.

Statistics

Data were analyzed using Stata, version 15.1 [40]. Relative risks (RR) were obtained using Cox regression, and we verified that the proportional hazards assumption was not violated. RR related to diagnostic criteria compares the rate of mortality in criteria positive subjects to the rate in criteria negative persons. For non-criteria variables the comparison is between those with the characteristic to those without the characteristic. It is medically relevant to ask how much of the variation in the outcome (survival time) is accounted for through the prognostic index [41]. A covariate with a 'large' estimated regression coefficient is of little predictive value if it has almost no variability in the population from which the sample was draw [42]. The explained variance (R2) of our models was estimated by methods described by Royston and Sauerbrei [41]. R2 is a universally adopted measure of predictive ability. It is the proportion of variability in the outcome that is explained through the model covariates. R2 values range from 0 to 1 with higher values indicating better predictive ability [43]. We used the Stata program str2d to obtain these statistics.

SMRs compare mortality rates in the study population to a standardized US population. To determine SMRs from survival analyses, we used the Stata strate procedure and age-, sex -and calendar-stratified reference mortality rates from the US general population [44]. Cause-specific mortality data were obtained from National Vital Statistics Reports for 2006 [45]. We calculated the standardized mortality odds ratio (OR) based on the age- and sex-stratified number of deaths from underlying specific causes in the general population and in study participants.

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

The characteristics of the four study groups (RA, NIRMD, clinical FM, and all patients) are described in Table 1. Patient ages range from 21 to 103 years. The groups differ in age and sex, and in the percent of patients who satisfy FM 2016 criteria. In particular, 63% of clinical FM patients satisfy FM 2016 criteria compared with 22.9% and 18.3% of RA and NIRMD patients. The death rates are also different, reflecting differences in age and sex, as well as the innate severity of the RA group.

Table 2 displays the SMRs and RRs for all of the clinical groups. The RR represents the effect of the 2016 FM criteria on mortality, adjusted for age and sex. A central finding of this table is that the SMR for RA 1.26 (1.23–1.29) is substantially greater than the SMRs for the NIRMD and clinical FM groups, whether or not patients are FM 2016 positive or FM 2016 negative, a reflection of the seriousness of RA. By contrast, RRs for the three disorders are similar and increased above unity: RA 1.52 (1.43–1.61), NIRMD 1.43 (1.24–1.66) and clinical FM 1.41 (1.14–1.75). This indicates that criteria positive FM is associated with an increased risk for mortality regardless of associated or underlying diagnosis.

Because the literature associates FM and WSP criteria with mortality risk using different definition and with different results, we compared some of the different definitions in Table 3. By SMR and RR, the ACR 1990 definition had the weakest effect of the WSP definitions, with an RR of 1.19 (1.15–1.24) compared with 1.28

Table 1
The association of fibromyalgia (FM) diagnostic status and mortality.

Category	All patients	RA patients	NIRMD patients	Clinical FM
Subjects in group	35,248	26,458	5167	3659
Age, mean (SD) years	62.1 (13.7)	61.8 (14.7)	67.0 (12.9)	56.8 (12.8)
Female (%)	80.7	78.9	80.0	95.0
Cumulative FM 2016* over groups,%	100.0	75.0	14.6	10.4
FM Cases per category (%)	26.4	22.9	18.3	63.0
Deaths	8192	6609	1205	378
Death rate per 1000 persons-years (95% CI)	25.1 (24.5–25.6)	27.1 (26.4–27.7)	25.5 (24.1–27.0)	10.6 (9.6–11.8)
Years of observation	326,713	190,391	47,163	35,445

* By FM 2016 criteria. RA = rheumatoid arthritis, NIRMD = non-inflammatory rheumatic diseases, Clinical FM = Clinical diagnosis of FM by physician. CI = Confidence interval.

Table 2
Disease specific standardized mortality rates (SMR) and associations with FM criteria.

Diagnostic groups	All patients subset SMR (95%CI)	FM 2016+ subset SMR (95%CI)	FM 2016- subset SMR (95%CI)	RR (95% CI)*
All	1.10 (1.08–1.28)	1.48 (1.41–1.54)	1.02 (1.00–1.07)	1.38 (1.31–1.46)
RA	1.26 (1.23–1.29)	1.77 (1.69–1.87)	1.18 (1.15–1.21)	1.52 (1.43–1.61)
NIRMD	0.72 (0.69–0.77)	1.00 (0.86–1.12)	0.70 (0.66–0.74)	1.43 (1.24–1.66)
Clinical FM	0.76 (0.68–0.84)	0.91 (0.80–1.04)	0.60 (0.52–0.70)	1.41 (1.14–1.75)

* Adjusted for age and sex. SMR = standardized mortality ratio. RR = Relative risk for FM 2016. RA = rheumatoid arthritis, NIRMD = non-inflammatory rheumatic diseases, Clinical FM = Clinical diagnosis of FM by physician.

Table 3
The effect of different measures of FM and widespread pain on SMR, RR and variability (R2) for all subjects.

	SMR	RR (Cox regression)	Explained variance (R^2)
Baseline age and sex explained variance			0.255 (0.243–0.265)
1990 ACR WSP	1.22 (1.19–1.26)	1.19 (1.15–1.24)	0.259 (0.248–0.270)
2016 WSP	1.29 (1.24–1.33)	1.28 (1.23–1.36)	0.261 (0.250–0.272)
2019 WSP	1.33 (1.28–1.38)	1.29 (1.22–1.33)	0.262 (0.250–0.273)
FM 2011	1.45 (1.39–1.52)	1.37 (1.30–1.44)	0.264 (0.253–0.276)
FM 2016	1.48 (1.41–1.54)	1.38 (1.31–1.46)	0.264 (0.252–0.276)
PSD categories			0.268 (0.257–0.280)
None (0–3)	0.85 (0.81–0.90	0.74 (0.70–0.78)	
Mild (4–7)	0.99 (0.95–1.04)	0.89 (0.85–0.94)	
Moderate (8–11)	1.15 (1.10–1.21)	1.04 (0.99–1.10)	
Severe (12–19)	1.29 (1.23–1.35)	1.20 (1.14–1.27)	
Very severe (20–31)	1.56 (1.47–1.66)	1.37 (1.28–1.46)	

Baseline predictors of R^2 are adjusted for age and sex. RA = rheumatoid arthritis, NIRMD = non-inflammatory rheumatic diseases, Clinical FM = Clinical diagnosis of FM by physician. FM 2016 = FM 2016 criteria; FM 2011 = FM 2011 criteria; WSP = widespread pain. R2 = proportion of explained variation. RR = Relative risk.

(1.23–1.36) for the WSP definition used in FM 2016. The respective R2s were 0.259 and 0.264—which represents the sum of the baseline age and sex R2 0.255 (0.243–0.265) and the FM and WSP criteria components. Although, never used for assessment of mortality previously, the categorized continuous PSD scale represents a statistically stronger association with mortality than the other dichotomous criterions, as suggested by the R2 variability criterion (0.268). The PSD data also show that increasing PSD scores are associated with greater risk of mortality. We also present data for the newly described 2019 WSP definition, which performed similarly to 2016 WSP. The FM definitions (2016 and 2011) were marginally stronger compared to the WSP definitions in SMR and RR, with RRs of 1.38 (1.31–1.46) and 1.37 (1.30–1.44). In particular, the FM 2016 had a stronger effect and greater explained variance than the commonly used 1990 WSP criterion in SMR, RR and variability R2. Despite these differences, all of the R2 confidence intervals of the FM and WSP criteria variables were overlapping, indicating similar (limited) predictive ability.

Table 4 shows that almost all displayed "univariate" age and sex adjusted variables are associated with mortality, according to FM criteria status when all groups are considered together. Factors strongly associated with FM criteria positivity are age ≥65 (RR 9.11 (7.17–11.58)), current smoking (RR 2.10 (1.37–1.50)), high levels of HAQ (RR 5.72 (5.11–6.42)) and household income below the median (1.90 (1.48–2.49)). Important protective factors included being female and being married (0.54 (0.42–0.70)). No other variables had RRs ≥2 or ≤0.66. In a univariate analysis, ≥1 comorbid disorders

Table 4
Relative risk for mortality adjusted for age and sex.

	FM (+) Cases (% of subjects)	FM (-) Cases (% of subjects)	Mortality Univariate RR (95% CI) (adjusted for age) and sex)
FM 2016 (2016 criteria)	9300 (26.4)	25,984 (73.6)	1.38 (1.31–1.46)
College graduate	2323 (24.9)	8666 (33.4)	0.65 (0.62–0.69)
Female	8097 (87.1)	20,385 (78.4)	0.66 (0.63–0.69)
Age group			
21-<40 years	1008 (10.8)	2035 (7.8)	Reference
40–65 years	6209 (66.8)	14,144 (54.4)	4.57 (3.65–5.73)
≥65 years	2083 (22.4)	9805 (37.7)	10.09 (7.82–13.01)
Smoking			
Never	4684 (50.4)	14,016 (53.9)	Reference
Past	2938 (31.6)	9055 (34.9)	1.25 (1.19–1.31)
Current	1678 (18.0)	2913 (11.2)	2.10 (1.37–1.50)
Body mass index			
Underweight, <18.5 kg/m2	155 (1.7)	460 (1.8)	1.93 (1.69–2.20)
Normal weight, 18.5–24.9 kg/m2	2265 (25.4)	91.76 (35.1)	Reference
Overweight, 25.0–29.9 kg/m2	2676 (28.8)	8543 (32.9)	0.83 (0.78–0.87)
Obese, >30.0 kg/m2	4204 (45.2)	7805 (30.9)	0.96 (0.91–1.01)
HAQ (rounded to nearest integer)			
0.00 – 0.49	385 (4.1)	8282 (31.9)	Reference
0.50 – 1.49	3446 (37.1)	12,074 (46.5)	1.52 (1.43–1.62)
1.50 – 2.49	5011 (53.8)	5319 (20.5)	2.64 (2.46–2.81)
2.50 – 3.00	461 (5.0)	309 (1.2)	5.72 (5.11–6.41)
Depression, current	3731 (40.1)	3240 (12.5)	1.36 (1.28–1.45)
Cancer, current	174 (1.9)	438 (1.7)	1.75 (1.54–2.00)
Diabetes, current	1242 (13.5)	2064 (7.9)	1.67 (1.56–1.78)
Cardiovascular, current	1127 (12.1)	1898 (7.3)	1.62 (1.52–1.72)
Pulmonary, current	1931 (20.8)	2613 (10.1)	1.80 (1.70–1.92)
Renal, current	386 (4.2)	495 (1.9)	1.85 (1.64–2.09)
All opioids, current	4368 (49.0)	5748 (22.8)	1.44 (1.37–1.51)
Strong opioids, current	1004 (11.3)	856 (3.4)	1.87 (1.70–2.06)
NSAIDs, current	5488 (61.5)	15,689 (62.0)	0.78 (0.74–0.81)
Below median household income*	4901 (52.7)	9996 (38.5)	1.90 (1.48–2.49)
Married*	6091 (65.5)	17,952 (69.1)	0.54 (0.42–0.70)

* Not included in Table 5.
HAQ = Health assessment questionnaire disability index rounded to nearest whole number. NSAIDs = non-steroidal anti-inflammatory drugs. RR = Relative risk.

compared with no comorbid conditions had an RR of 1.55 (1.49–1.62). In the multivariable model (Model 1) of Table 5 this result was 1.43 (1.37–1.50).

We then used variables of Table 4 in the all groups multivariable analytic models in Table 5, except for income and marital status. Model 1 includes FM 2016, but omits HAQ functional disability status. The RR for FM is 1.15, and the R2 is 0.378. The RR for FM 2016 is reduced from 1.38 (1.31–1.46) in the univariate model to 1.15 (1.09–1.22), representing the effect of the simultaneous covariates in the multivariable model. In Model 2 we added a categorical version of the HAQ. In Model 3 we removed FM 2016 from the Model 2. R2 for Models 1, 2 and 3 were 0.378, 0.408 and 0.407, indicating that adding HAQ as an explanatory variable improves the models' explanatory power. When FM 2016 is removed (Model 3) the explanatory effect is not reduced. In Model 2, the addition of HAQ results in an RR for FM 2016 <1, 0.92 (0.87–0.98). Replacing all of the comorbidity variables in Model 1 with a binary 0/1 comorbidity variable result in an R2 of 0.362, and using all comorbidity items in a score results in an R2 of 0.361. We analyzed income and marital status separately because of their somewhat different nature. Addition of income and marital status resulted in an increase in R2 of model 1 from 0.378 (0.366–0.392 to 0.389 (0.380–0.403). With removal of FM 2016 the R2 was reduced to 0.389 (0.378–0.403).

Table 6 simultaneously compares HAQ functional disability and FM status. At medium and severe HAQ impairment, FM 2016+ reduces the RR, while FM 2016- increases the RR 1.97 (1.81–2.15) vs 2.21(2.05–2.38) and 3.62 (3.11–4.21) vs 4.25 (3.63–4.97). At minimal HAQ impairment FM 2016+ results in a protective effect on mortality hazard. These data indicate disagreements between functional severity and FM status, with the analyses favoring the effect of HAQ values. These analyses also explain the "protective" effect of FM 2016 on mortality hazard of model 2 in Table 5. In addition, a comparison of FM 2016 and HAQ functional status only but adjusted for age and sex shows that the HAQ model explains more variance, R2 0.330 vs. 0.263.

In Table 7 we examined cause specific mortality. Of the 20 cause specific conditions available, 5 were statistically significant in the combined group analysis. There was an increased risk of death from suicides (3.01 (1.55–5.84)), accidents (1.45 (1.11–1.91)), diabetes (1.78 (1.16–2.71) and hypertension related disorders (2.12 (1.20–3.74)), with positive odds ratios across the diagnostic groups. Overall, patients with FM were less likely to die from cancer (0.77 (0.68–0.88)).

Table 6
The combined effect of FM2016 status and HAQ categories on mortality relative risk.

HAQ and FM Categories HAQ severity category	FM status	Relative Risk (95% CI)
Minimal impairment (0.00 – 0.49	FM-	Reference
Minimal impairment (0.00 – 0.49)	FM+	0.98 (0.71–1.35)
Low impairment (0.50 – 1.49)	FM-	1.43 (1.34–1.53)
Low impairment (0.50 – 1.49)	FM+	1.42 (1.28–1.58)
Medium impairment (1.50 – 2.49)	FM-	2.21(2.05–2.38)
Medium impairment (1.50 – 2.49)	FM+	1.97 (1.81–2.15)
Severe impairment (2.50 – 3.00)	FM-	4.25 (3.63–4.97)
Severe impairment (2.50 – 3.00)	FM+	3.62 (3.11–4.21)

Model of Table 6 is the same as Model 2 except that a single combined FM2016-HAQ group replaces the two individual FM2016 and HAQ group variables. R^2 statistic is 0.404 (0.391–0.417).

Table 5
Multivariable models of the association of fibromyalgia status with mortality.

Model	Model 1 Full Relative risk (95% CI)	Model 2 Full + HAQ Relative risk (95% CI)	Model 3 Full +HAQ –FM 2016 Relative risk (95% CI)
FM 2016 (2016 criteria)	1.15 (1.09–1.22)	0.92 (0.87–0.98)	
Female	0.67 (0.64–0.70)	0.58 (0.55–0.61)	0.58 (0.55–0.61)
Age group			
21-<40 years	Reference	Reference	Reference
40–65 years	4.49 (3.78–5.63)	4.25 (3.39–5.53)	4.26 (3.40–5.34)
≥65 years	22.32 (18.06–27.58)	19.87 (15.66–24.88)	20.08 (16.04–25.15)
College graduate	0.77 (0.73–0.81)	0.34 (0.78–0.8)	0.83 (0.78–0.87)
Smoking			
Never	Reference	Reference	Reference
Past	1.15 (1.10–1.21)	1.16 (1.11–1.22)	1.15 (1.10–1.21)
Current	1.80 (1.68–1.93)	1.79 (1.68–1.92)	1.79 (1.68–1.91)
Body mass index			
Underweight, <18.5 kg/m2	1.68 (1.47–1.92)	1.48 (1.30–1.69)	1.49 (1.30–1.70)
Normal weight, 18.5–24.9 kg/m2	Reference		Reference
Overweight, 25.0–29.9 kg/m2	0.82 (0.78–0.87)	0.82 (0.78–0.86)	0.82 (0.78–0.86)
Obese, >30.0 kg/m2	0.86 (0.81–0.91)	0.82 (0.78–0.87)	0.82 (0.77–0.87)
HAQ category			
0.00 – 0.49	Reference	Reference	Reference
0.50 – 1.49		1.44 (1.35–1.54)	1.43 (1.34–1.53)
1.50 – 2.49		2.18 (2.03–2.34)	2.13 (1.98–2.28)
2.50 – 3.00		4.06 (3.60–4.58)	3.92 (3.48–4.41)
Depression, current	1.08 (1.00–1.13)	1.02 (0.96–1.09)	1.01 (0.94–1.07)
Cancer, current	1.57 (1.38–1.78)	1.58 (1.39–1.80)	1.58 (1.39–1.79)
Diabetes, current	1.46 (1.36–1.56)	1.50 (1.31–1.50)	1.40 (1.30–1.49)
Cardiovascular, current	1.39 (1.30–1.48)	1.35 (1.26–1.44)	1.34 (1.26–1.42)
Pulmonary, current	1.53 (1.44–1.63)	1.47 (1.38–1.56)	1.46 (1.38–1.56)
Renal, current	1.38 (1.22–1.55)	1.31 (1.16–1.40)	1.31 (1.16–1.48)
All opioids, current	1.25 (1.18–1.31)	1.12 (1.05–1.18)	1.11 (1.06–1.17)
Strong opioids, current	1.33 (1.20–1.48)	1.26 (1.13–1.39)	1.25 (1.13–1.39)
NSAIDs, current	0.86 (0.82–0.90)	0.85 (0.81–0.89)	0.85 (0.81–0.89)
Rheumatoid arthritis (RA)	1.55 (1.47–1.64)	1.41 (1.33–1.49)	1.42 (1.34–1.50)
R^2 statistic	0.378 (0.366–0.392)	0.408 (0.396–0.422)	0.407 (0.396–0.421)

HAQ = Health assessment questionnaire disability index rounded to nearest whole number. NSAIDs = non-steroidal anti-inflammatory drugs.

Table 7
Death causes related to FM 2016 criteria diagnosis as OR (95% CI) by diagnosis group.

Primary cause of death	Deaths	%	All	RA	NIRMD	FM
Number of patients			35,284	26,458	5167	3659
Diseases of heart	2347	25.88	1.01 (0.91–1.13)	1.02 (0.90–1.15)	1.14 (0.84–1.54)	1.49 ().72–1.84)
Malignant neoplasms	1902	20.97	0.77 (0.68–0.88)*	0.77 (0.66–0.88)*	0.73 (0.52–1.02)	0.70 (0.45–1.11)
Cerebrovascular diseases	535	5.90	0.86 (0.70–1.06)	0.75 (0.68–0.96)*	1.00 (0.57–1.75)	1.47 (0.68–3.17)
Chronic lower respiratory diseases	749	8.26	1.04 (0.88–1.24)	1.02 (0.84–1.23)	1.54 (0.86–2.77)	0.87 (0.41–1.88)
Accidents (unintentional injuries)	253	2.79	1.45 (1.11–1.91)*	1.42 (1.04–1.93)*	1.15 (0.52–2.53)	2.78 (0.78–9.90)
Alzheimer's disease	324	3.57	0.99 (0.76–1.28)	1.01 (0.74–1.38)	0.85 (0.45–1.60)	1.06 (0.41–2.77)
Diabetes Mellitus	95	1.05	1.78 (1.16–2,71)*	1.77 (1.11–2.85)*	3.16 (1.19–8.39)*	0.62 (0.04–9.99)
Influenza and pneumonia	589	6.50	1.06 (0.87–1.28)	1.08 (0.88–1.34)	0.90 (0.43–1.87)	0.97 (0.41–2.28)
Nephritis/nephrotic syndrome/nephrosis	201	2.22	0.99 (0.72–1.38)	1.07 (0.85–1.53)	1.16 (0.47–2.88)	0.30 (0.07–1.22)
Septicemia	536	5.91	1.16 (0.95–1.42)	1.25 (1.01–1.55)*	1.96 (0.54–2.08)	0.45 (0.22–1.37)
Intentional self-harm (suicide)	35	0.39	3.01 (1.55–5.84)*	2.12 (0.96–4.68)	8.71 (1.80–42.08)*[b]	4.42 (0.54–36.43)
Chronic liver disease and cirrhosis	75	0.83	0.86 (0.49–1,49)	0.90 (0.49–1.66)	1.27 (0.26–6.14)	0.20 (0.21–1.98)
Hypertension/hypertensive renal disease	50	0.55	2.12 (1.20–3.74)*	2.01 (1.01–3.99)	1.11 (0.23–5.25)	2.16 (0.78–9.00)[b]
Parkinson's disease	46	0.51	0.57 (0.25–1.27)	0.50 (0.17–1.43)	0.80 (0.18–2.65)	0.62 (0.04–9.98)
Assault (homicide)	8	0.09	3.17 (0.79–12.69)	0.85 (0.09–7.57)		
Other	488	5.38	1.33 (1.09–1.63)	1.43 (1.14–1.79)	1.14 (0.62–2.08)	1.38 (0.47–4.06)
Lower GI	67	0.74	1.55 (0.93–2.59)	1.04 (0.56–1.96)	6.71 (1.12–40.39)*	3.79 (0.45–31.79)
Other Infections	227	2.50	1.06 (078–1.44)	1.04 (0.74–1.47)	0.93 (0.31–2.76)	0.99 (0.31–3.09)
Upper GI/Bleed/Ulcer	46	0.51	0.57 (0.25–1.27)	0.58 (0.25–1.38)	1.11 (0.12–9.95)	1.56 (0.30–8.16)
Vascular/Vasculitis/Embolism/Blood Clot	236	2.60	0.80 (0.5801.08)	0.90 (0.63–1.29)	0.43 (1.15–1.22)	0.30 (0.3–3.42)
Missing/No Death cause	229	2.53	0.93 (0.68–1.27)	0.98 (0.69–1.38)	0.61 (0.80–2.16)	0.61 (0.17–2.15)
Unknown	30	0.33	1.58 (0.74–3.39)	NE	0.41 (0.05–3.40)[b]	0.33 (0.03–3.42)
Total	9068	100.0				

* $p < 0.05$. [B] = NIRMD and FM together. NE = Not estimable. OR = Odds ratio.

Discussion

The data of this study show that FM is positively associated with the risk of mortality, with unadjusted and adjusted relative risks of 1.38 (1.31–1.46) and 1.15 (1.09–1.22) (Tables 4 and 5). The measures of FM mortality risk also extend to individual diagnostic groups, including RA, OA and clinical FM (diagnoses made by a physician - not determined only by criteria). Patients satisfying FM 2016 criteria in these groups all showed positive associations with mortality. SMRs, however, provide different information. SMRs were increased in RA, but decreased in NIRMD and in clinically diagnosed FM. SMR data reflect factors beyond the effect of FM. In RA, the SMR for all subjects was 1.26 (1.23–1.29), reflecting the medical severity of RA. In clinical FM and NIRMD, the SMR was less than 1. This likely reflects both the lessor systemic seriousness of NIRMD and clinical FM on mortality as well as inherent referral differences. Persons likely to participate in complex long term surveys have increased education and social status, components that are known to associate with increased survival [46]. In the absence of a representative sample, SMR comparisons only relate to the individual samples under study and cannot be generalized [24–26]. RR, therefore, provides a better estimate of the effect of FM 2016 criteria as it is unbiased with respect to the group under study.

We also found that clinical FM was not a homogenous group, as only 63.0% satisfied FM criteria. In the criteria positive vs. criteria negative clinical FM group the mortality RR was 1.41 (1.14–1.75) with respect to FM 2016 criteria. These data also suggest to us that the belief that clinical diagnosis of FM is the same and has the same meaning and effect as criteria-based diagnosis is incorrect. Multiple US studies now show high levels of misclassification of FM, with up to 75% of diagnosed cases not meeting criteria, underscoring the importance of this observation [17–20]. These are US studies, as no similar studies have been done elsewhere. We have previously suggested that, with respect to clinical measurements, "primary and secondary fibromyalgia are the same" [47]. Our current data now show that with respect to mortality primary FM acts similarly as FM occurring in other medical diseases.

Because mortality is an objective measure, we were able to compare various definitions of FM and WSP criteria. The FM 2016 and FM 2011 criteria produce the highest SMR and RR estimates and the 1990 ACR WSP criteria the lowest estimate. Among the WSP definitions, the recently suggested 2019 WSP criteria and the 2016 WSP definition appear to have the highest RR and the variability R2 scores [31]. Even so, FM and WSP variables explain only a fraction of model variance, as baseline R2 is 0.255 while 1990 WSP is 0.258, a 0.003 unit difference, and 2016 criteria is 0.264, an increase of 0.009 units. Moreover, the upper 95% confidence interval of the baseline model overlaps with every criteria definition confidence interval except for PSD categories, and the confidence intervals of all of the specific criteria overlap. These data indicate that with respect to predicting mortality all criteria are about equal and all are poor predictors of mortality. The explained variance of FM 2016 in the all-patient model is (0.264–0.255)/0.264 or <4%. For technical reasons we were unable to include the recently described "AAPT" FM criteria in this study [48], however, analyses of limited samples suggested that these criteria performed similarly to the FM criteria of Table 3 (data not shown).

Our data also suggest that a continuous scale, such as the polysymptomatic distress scale [31], provides a graduated estimate of mortality risk. This observation is in accord with the observation that it is not just whether or not one satisfies FM criteria that is most important in regard to mortality, but rather the extent to which FM symptoms are present [34,49]. As shown in Table 3, the RR increases from 1.20 to 1.37 as the PSD score changes from severe (12–19) to very severe (20–31), with an explained variance of 0.268 (0.257–0.280). There appears to be a useful advantage to thinking about FM in terms of the PSD [50].

The data from the multivariable analyses of Table 5 provide insights into the relation of other variables to the issue of mortality as well as to the definition and meaning of FM. College education, smoking status, opioid use, comorbid illnesses and obesity have all been shown previously to be associated with FM. Excluding body mass index in this case, one possible interpretation of Table 5 is that these variables share common variance with FM and that is why the RR for FM is reduced to 1.15 (1.09–1.22). Obesity, however is negatively associated with mortality in these analyses. It is not clear why this is the case because regression of obesity on FM shows a strong association (odds ratio, adjusted for age and sex = 1.73 (1.64–1.83)). However, other studies have shown a "protective effect" of increased BMI on mortality [51].

Among the important problems raised by data from Tables 5 and 6 is the effect of functional status on mortality and the relation between functional status, as measured by the HAQ disability index,

and FM 2016. As shown in Table 5, the HAQ RRs are the strongest of all variables – a high as 4.06 in the most functionally disabled category. When the HAQ is introduced into Model, the FM 2016 RR changes to <1 (0.92 (0.87–0.98)) and the R2 statistic increases from 0.378 to 0.408. That is, Model 2 seems to be a better model that Model 1. In Model 3 we remove FM 2016 and the R2 remains about the same as in Model 2 (0.407). We investigated this in Table 6 by pairing all levels of HAQ with each level of FM 2016. Overall, the data of this table show that at every level of HAQ persons FM 2016 positive show less association with mortality than patients who are FM 2016 negative. One possibility for this finding is that persons with FM 2016 report more severe symptoms than they would be expected to have, given their HAQ status, particularly in view of the higher R2 statistics in Models 2 and 3. We did not include reduced household income and marital status in Table 5 as it was uncertain if these more external factors should be included, as they would alter the RR data of the table. However, data from Table 4 shows that they had relatively influential RRs. Separately, we calculated that if they were added to Model 1 of Table 5 they would increase the explained variance from 0.378 to 0.389.

It is of some interest that we found evidence of cause-specific mortality for suicide and accidents in FM 2016 positive patients. While this was found for clinical FM patients in our previous study [3], the current study supports this finding in FM positive RA and NIRMD patients as well. Mortality from suicide has been found by others [52]. In a Danish study of 1361 FM patients over 15 years, no overall increase in mortality was found, however in the 1269 female patients, the SMR for an increased risk of death from suicide, was 10.5 (95% CI 4.5–20.7) [4]. Macfarlane also noted more deaths from accidents, suicide, violence) among people with widespread pain (5.21, 0.94 to 28.78) [7]. We found a protective effect of FM diagnosis for cancer, but the opposite was found in another large study of WSP [9].

Although not shown in detail in our report, analysis of current data with a WSP criterion rather than FM 2016 did not change our results, with an all-cause age and sex adjusted RR of 1.19 (1.15–1.24). The mortality risk ratio (MRR) in the 2017 UK study of WSP and mortality was 2.43 (95%CI 2.17–2.72), compared with our age and sex adjusted FM RR of 1.38 (1.31–1.46). The MacFarlane 2107 paper also includes a meta analysis of 6 WSP studies which yielded with a pooled MRR of 1.63 (0.98–270) [9]. The reasons for study differences are not clear, but differences may occur because of definition of WSP or FM, methods of analysis, follow-up time, methods of recruitment and subject samples [5].

Our study has a number of limitations. It was not-population-based, but enrolled patients with rheumatic diseases who were willing to participant in surveys. Because our study used only entry data, we were unable to examine complex drug use and drug continuation and switching. We found no association between NSAID use and mortality, and that was because all patients in these groups used NSAIDs at comparable rates. We found weak associations with opioids, association which may have been markers for the complex severity of FM. If opioids were in fact harmful but not lethal, our data would have been insufficient to detect such associations. Over the 15 years of the study patients may have may have changed FM positive or negative status. However, this is a factor in essentially all WSP studies, too.

In summary, we have shown that FM and WSP are associated with mortality and that such an association can be seen in other specific disorders, such as RA and NIRMD. Clinical FM can be split into criteria positive and criteria negative states, but positive associations with mortality only occur in criteria positive states. Many definitions of FM and WSP will identify mortality, but the greatest RR appeared to be with the 2016 criteria or with the infrequently used categories of the PSD scale. When covariates are added to multivariable analyses, the effect of FM criteria diagnosis remains, but is reduced. There is a discordance between the effect on mortality of FM 2016 and HAQ functional status that suggests the possibility of over-reporting distress in patients with FM, an effect that we have noted elsewhere [53]. Finally, the effect of FM and WSP on mortality is weak, explaining <4% of explained variance. On an etiologic basis, it remains uncertain whether fibromyalgia as an entity contributes to mortality or is just conduit for underlying associated physical and mental stressors.

Declaration of competing interest

The authors declare no conflicts of interest.

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