RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Fibromyalgia and mortality: a systematic review and meta-analysis

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To cite: Treister-Goltzman Y, Peleg R. Fibromyalgia and mortality: a systematic review and meta-analysis. *RMD Open* 2023;**9**:e003005. doi:10.1136/rmdopen-2023-003005

Received 16 January 2023
Accepted 19 May 2023

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ABSTRACT

Objective To conduct a systematic review of the literature on the association between fibromyalgia and mortality and to pool the results in a meta-analysis.

Methods The authors searched the PubMed, Scopus, and Web of Science databases using the key words 'fibromyalgia' and 'mortality' to identify studies that addressed an association between fibromyalgia and mortality. Original papers that assessed associations between fibromyalgia and mortality (all or specific causes) and provided an effect measure (hazard ratio (HR), standardised mortality ratio (SMR), odds ratio (OR)) quantifying the relationship between fibromyalgia and mortality were included in the systematic review. Of 557 papers that were initially identified using the search words, 8 papers were considered eligible for the systematic review and meta-analysis. We used a Newcastle-Ottawa scale to assess the risk of bias in the studies.

Results The total fibromyalgia group included 188 751 patients. An increased HR was found for all-cause mortality (HR 1.27, 95% CI 1.04 to 1.51), but not for the subgroup diagnosed by the 1990 criteria. There was a borderline increased SMR for accidents (SMR 1.95, 95% CI 0.97 to 3.92), an increased risk for mortality from infections (SMR 1.66, 95% CI 1.15 to 2.38), and suicide (SMR 3.37, 95% CI 1.52 to 7.50), and a decreased mortality rate for cancer (SMR 0.82, 95% CI 0.69 to 0.97). The studies showed significant heterogeneity.

Conclusions These potential associations indicate that fibromyalgia should be taken seriously, with a special focus on screening for suicidal ideation, accident prevention, and the prevention and treatment of infections.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are reports on the association of widespread pain, the central criteria for fibromyalgia, and increased mortality rates. To date there is no consensus as to whether fibromyalgia is associated with increased mortality.

WHAT THIS STUDY ADDS

⇒ Our meta-analysis showed an increased risk for all-cause mortality (HR 1.27). There was a borderline increased risk for accidents (SMR 1.95), an increased risk for mortality from infections (SMR 1.66), and suicide (SMR 3.37), and a decreased mortality rate for cancer (SMR 0.82).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results show that attention should be focused on screening for suicidal ideation, accident prevention, and prevention and treatment of infections among fibromyalgia patients.

INTRODUCTION

Fibromyalgia is a poorly understood disease whose prevalence has increased over the years.[1 2] The diagnostic criteria have evolved since 1990 in parallel with an enhanced understanding of its clinical manifestations, from widespread pain and tender points on clinical examination,[3] to fibromyalgia as a polysymptomatic disorder in the 2010 and 2011 criteria,[4 5] and to the 2016 criteria that incorporates modified widespread pain, with improved specificity.[4 5] There is a growing understanding that fibromyalgia coexists with other health problems including other rheumatic diseases, and gastrointestinal, neurologic and mental health disorders.[6–8] A recent study showed a positive association between the number of comorbid conditions and the severity of fibromyalgia symptoms.[9] In light of the high burden of comorbidity, fibromyalgia patients could suffer from increased mortality. This hypothesis is strengthened by reports of the association of the widespread pain—the central criteria for fibromyalgia—and increased mortality rates for all-causes, cardiovascular and cancer mortality,[10 11] and suicide attempts.[12] To date there is no consensus as to whether fibromyalgia is associated with increased mortality. The purpose of the present study was to conduct a systematic review of the existing literature on the association between clinical fibromyalgia and mortality, either all-cause or specific, and to pool the results in a meta-analysis.

METHODS

Data sources and searches

The authors searched PubMed, Scopus, and the Web of Science electronic databases in

August 2022 to identify studies that addressed associations between fibromyalgia and mortality. The search was conducted using the key words 'fibromyalgia' and 'mortality'. There was no limitation by date or language of publication. To identify additional studies, we reviewed the bibliographies of the full text papers that were included in the systematic review.

To ensure that the studies introduced into the review included patients with fibromyalgia, we selected studies that used the following fibromyalgia definitions:

1. In studies in which the diagnosis of fibromyalgia was extracted from medical records, the International Classification of Diseases and Injuries (ICD) codes 729.1 (for version 9) and M79.7 (for version 10) were used.
2. In studies in which the diagnosis of fibromyalgia was verified by interview/physical examination, the American College of Rheumatology (ACR) criteria (versions 1990, 2010, 2011, or 2016), or referring rheumatologist diagnosis by criteria in effect at the time of enrolment, if before 1990, were used.

Although the criteria for fibromyalgia have evolved over the years and may identify different sets of patients, the strategy adopted was deemed appropriate since the aim of our review focused on question of whether clinical, real-life cohorts of fibromyalgia patients suffer from excess mortality. In real-life clinical practice, fibromyalgia patients are a mixed population, diagnosed in different years by different criteria relevant at the time of diagnosis, who were diagnosed by rheumatologists or family physicians.

Study selection

The search for suitable studies was conducted in two phases according to the a priori inclusion and exclusion criteria. The following criteria were used to include papers in the systematic review: (1) original research that assessed associations between fibromyalgia and mortality (either all-cause or specific-cause); (2) the definition or the diagnosis of fibromyalgia was made as detailed above; and (3) the study provided effect measures (hazard ratio (HR), standardised mortality ratio (SMR), odds ratio (OR)) quantifying the relationship between fibromyalgia and mortality.

The following criteria were used to exclude papers from the review: (1) studies that were not original research, for example, reviews or case reports; (2) papers that related to widespread pain, either short- or long-term; and (3) not a fibromyalgia diagnosis.

In the first phase, all the abstracts were evaluated for inclusion and exclusion criteria. This phase was carried out by a single investigator (YTG). In the second phase, both investigators read the full texts of the selected abstracts chosen in the first phase and conducted a comprehensive, independent review of all the papers in their bibliographies to identify potentially relevant papers. In cases of disagreement the paper was discussed until a joint decision was reached.

Data extraction

The two investigators independently extracted data relevant to the study aim. All discrepancies were resolved by discussion. The data recorded included the authors and the year of publication, the age and origin of the participating patients, the sample size of the study population, the method of diagnosis of fibromyalgia, the type of fibromyalgia, the method of mortality confirmation, the type of assessed mortality (all-cause, specific causes), and quantitative assessment of mortality (HR, SMR, OR).

The effect measures (HR, SMR, OR) extracted from the eligible studies were adjusted for age and sex, but not for other potential confounding factors, such as the Charlson score or concomitant psychiatric conditions, since the main aim of the review was to assess whether there is an increased mortality risk in fibromyalgia patients, and not whether fibromyalgia per se, in fully adjusted effect measures, leads to increased mortality.

Quality assessment

We used a Newcastle-Ottawa scale to assess the risk of bias in the included studies.[13] The Newcastle-Ottawa scale is a simple, convenient tool for the quality assessment of non-randomised studies.[13] The Newcastle-Ottawa scale for cohort studies contains eight criteria. There are three criteria for selection bias assessment with a maximum of one star for each, one criterion for comparability assessment with a maximum of two stars, and three criteria for outcome bias assessment with a maximum of one star for each. The risk of bias assessment was carried out by the two investigators in a blinded process; in cases of disagreement a consensus process was used.

Data synthesis and analysis

The findings of the studies were grouped and described according to the type of assessed mortality (all-cause, specific causes). Meta-analyses were performed if more than two studies assessed the same type of mortality. The meta-analyses were performed using the inverse-variance method with Metafor, Meta and Demtar packages for R software (version 3.6.1).[14] As we anticipated considerable between-study heterogeneity, a random-effect model was used to pool effect sizes. Due to a binary effect size the Paule-Mandel estimator of the variance of the distribution of true effect sizes was the best choice.[15] Heterogeneity across the studies was assessed using the I^2 (inconsistency index) measure to describe the percentage of the variability of the effect due to heterogeneity. A value above 50% or $p<0.1$ indicated statistically significant heterogeneity.

RESULTS

Study selection

A total of 557 studies were identified in PubMed, CIANHL, Scopus, and Web of Science, using the predetermined key words. Of these, 150 were duplications. In the first stage of article selection 407 abstracts and paper titles were reviewed. Of these, 374 were excluded

because it was clear from the title and/or abstract that they did not meet the inclusion criteria. Thirty-three full text papers were checked in the second stage of article selection to determine if they met the inclusion or exclusion criteria. One of the papers was a short report of a meeting proceedings, for which the first author, in response to our request, sent us additional details on the study.[16] A review of the bibliographies of the full papers that were included in the second phase of the review did not produce any additional studies that fulfilled the inclusion and exclusion criteria. Thus, at the end of the screening process, eight papers[16–23] were entered into the systematic review and meta-analysis. The selection process is shown in figure 1.

The characteristics of the articles that were included in the review are shown in table 1. All were cohort studies published in English. The year of publication ranged between 1999 and 2021. Since follow-up periods varied from 16 to 31 years in studies that assessed all-cause

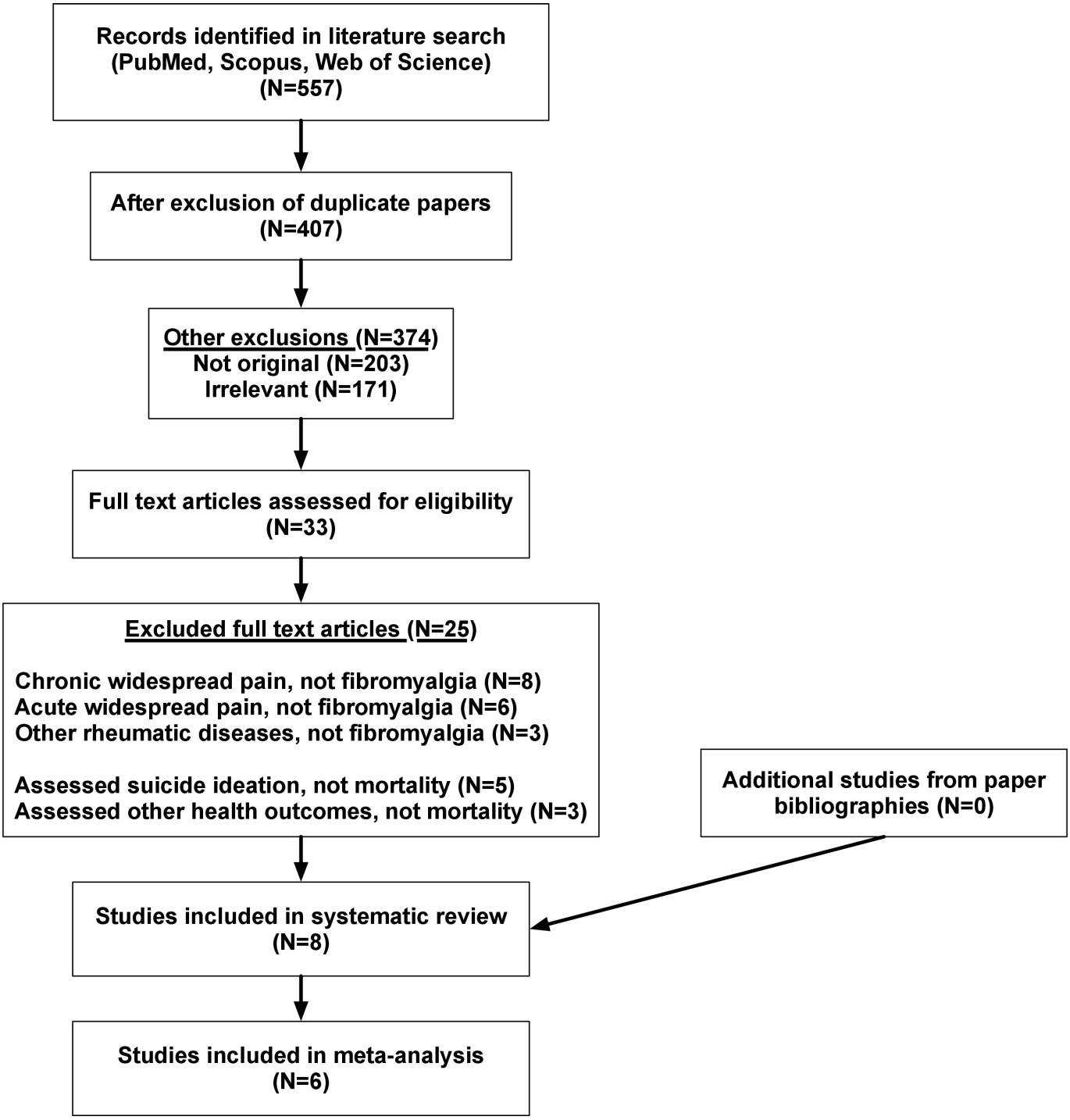

Figure 1 Flowchart of review process.

Table 1 Studies included in the systematic review and meta-analysis on the association between fibromyalgia and mortality

Study reference	Design	Participants	Female gender (%)	Age of participants	Length of follow-up	Criteria for fibromyalgia diagnosis	Type of fibromyalgia	Mortality ascertainment	Assessed mortality
Wolfe *et al*[16]	Cohort	1747 fibromyalgia patients from the community clinical rheumatology practice, compared with the general US population	87	Mean (SD) 51 (14)	25 years	ACR* (1990), or criteria in effect at the time of enrolment	Primary	US census data	All-cause mortality, mortality from specific causes (pneumonia, accident)
Dreyer *et al*[17]	Cohort	1320 Danish patients (1189 with confirmed fibromyalgia, and 131 with possible fibromyalgia), compared with the general Danish population	94	Age group (years) % 19–29 5 30–49 59 50–69 36 70+ 1	16 years, 5295 person-years, mean follow-up time 3.9 years	ACR* (1990)	Primary and secondary	Linkage to the Danish mortality register	All-cause mortality, mortality from specific causes (ischaemic heart disease, other heart disease, cerebrovascular disease, cancer, pneumonia, chronic obstructive pulmonary disease, liver cirrhosis/biliary tract disease, mental disorders, accident, suicide)
Markkula *et al*[18]	Cohort	1329 patients with probable fibromyalgia and 5928 control patients with no fibromyalgia symptoms, from a Finnish twin cohort	56	Mean (SD) 47 (8)	19 years	ACR* (1990)	Primary	Linkage to the Finnish population register centre	All-cause mortality

Continued

Table 1 Continued

Study reference	Design	Participants	Female gender (%)	Age of participants	Length of follow-up	Criteria for fibromyalgia diagnosis	Type of fibromyalgia	Mortality ascertainment	Assessed mortality
Wolfe *et al*[19]	Cohort	8186 fibromyalgia patients from several settings in the USA, diagnosed by a rheumatologist; controls: 10 087 osteoarthritis patients, and the general US population	94	Mean (SD) 51 (12)	31 years, 60 413 person-years, mean follow-up time 7.3 years	Referring rheumatologist diagnosis if before 1990, ACR* (1990), ACR* (2010) (predicted for part of the patients)	Primary	Families, physicians, confirmation by US National Death Index	All-cause mortality, mortality from specific causes (heart disease, malignancy, accident, chronic lower respiratory disease, pneumonia, septicaemia, suicide, cerebrovascular disease, kidney disease, hypertension, liver disease, Parkinson's disease, homicide)
Wolfe *et al*[20]	Cohort	3659 fibromyalgia patients from the National Data Bank for Rheumatic Diseases, USA, compared with a standardised US population	95	Mean (SD) 57 (13)	16 years, mean 9.3 years	Referring rheumatologist diagnosis, ACR* (2011), ACR* (2016) (predicted in part of patients)	Primary and secondary	US National Death Index	All-cause mortality, mortality from specific causes (heart disease, malignancy, accident, chronic lower respiratory disease, pneumonia, septicaemia, suicide, cerebrovascular disease, kidney disease, hypertension, liver disease, Parkinson's disease, homicide, lower GI diseases, upper GI disease/bleeding, vasculitis/blood clot)

Continued

Table 1 Continued

Study reference	Design	Participants	Female gender (%)	Age of participants	Length of follow-up	Criteria for fibromyalgia diagnosis	Type of fibromyalgia	Mortality ascertainment	Assessed mortality
Ilgen *et al*[21]	Cohort	79 359 patients from the Veterans Health Administration, USA; controls: patients from the same cohort without a pain condition	17	No data on age of fibromyalgia patients, age of the total cohort Age group: % 18–29: 3 30–49: 3 50–69: 16 ≥70: 43	3 years	ICD†-9 code (729.1) in medical record	Primary and secondary	US National Death Index, ICD†-10 code X60-X84, Y87.0	Suicide mortality
Hesler *et al*[22]	Cohort	89 589 fibromyalgia patients and 89 589 matched controls, hospitalised for surgical procedures in seven states in the USA	90	Mean (range) 61 (40–100)	NR	ICD†-9 code (729.1) in medical record	Primary and secondary	Discharge records	Perioperative in-hospital mortality
Singh *et al*[23]	Cohort	5309 patients with fibromyalgia, and 759 289 controls without fibromyalgia, hospitalised due to opioid use disorder from the US national inpatient sample data	79 (cases), 48 (controls)	Mean (SE) 51 (0.2) Age group: % <34: 10 34–45: 21 >45–55: 30 >5: 38	Mean (SE) hospital stay 3.7 (0.1) days; median-2.1 days	ICD†-9 code (729.1)/ ICD†-10 code (M79.7) in medical records	Primary and secondary	Discharge records	In-hospital opioid use disorder related mortality

*American College of Rheumatology criteria
†International Classification of Diseases
GI, gastrointestinal.

mortality, the diagnostic criteria for fibromyalgia varied, as in real life, from ACR versions 1990, 2010, 2011, and 2016 for the patients diagnosed after 1990, to the criteria in effect at the time of the study for patients diagnosed before 1990. In some studies different criteria were used for the patient populations in the same study.[16 19 20] In three studies the fibromyalgia definition was based on ICD-9 code (729.1)/ICD-10 code (M79.7) from medical records.[21–23] Three studies included patients with primary fibromyalgia only,[16 18 19] and the others[17 20–23] included patients with both primary and secondary types of fibromyalgia. There was great variance in sample size of the fibromyalgia groups, from 1320 in the study by Dreyer *et al*[17] to 89 589 in the study by Ilgen *et al*.[18] The entire fibromyalgia group numbered 188 751 patients. While most studies were clearly female preponderant, one study[18] had a mixed population and one study[21] was male preponderant. The mean age of the study polpulation, in most studies, was older than 50 years, with a slightly younger population in two studies.[17 18] The majority of studies were conducted in the USA,[16 19–23] one study[17] was conducted in Denmark, and one study[18] in Finland. Five studies[16–20] assessed all-cause mortality, four of which examined mortality from specific causes as well.[16 17 19 20] In one study mortality due to suicide was assessed,[21] in one study hospital mortality after surgical procedures was evaluated,[22] and in another study in-hospital mortality related to opioid use was investigated.[23] In some studies SMRs were calculated[16 17 19 20]—that is, mortality rates in fibromyalgia patients were compared with mortality rates in a standardised population from the same country—and in others patients without fibromyalgia from the same setting served as the control group.[18 21 23] In one study both approaches were used.[19]

Outcomes: all-cause mortality

Two of the three studies that examined HR for all-cause mortality of fibromyalgia patients compared with patients from the same or a similar setting without fibromyalgia found an increased HR[18 20]; in one study the difference did not reach statistical significance.[19] Of the four studies that calculated SMR, one found an increased mortality rate,[16] one found a decreased rate,[20] and two studies[17 19] showed no significant difference in mortality rates for fibromyalgia patients compared with a standardised population. When the results of the studies were pooled in the meta-analyses (figure 2), there was an increased HR for mortality (HR 1.27, 95% CI 1.04 to 1.51), with significant heterogeneity between the studies (I^2 91%, p<0.01), but no increase in SMR (SMR 1.07, 95% CI 0.74 to 1.39) with significant heterogeneity between the studies (I^2 85%, p<0.01)

Outcomes: mortality from specific causes

The results of individual studies and meta-analyses of subgroups on different causes of mortality in fibromyalgia patients are presented in figure 3. Pooled SMRs for heart, cerebrovascular, chronic lower respiratory, and chronic liver diseases were not statistically significant and all had significant heterogeneity between the studies. The SMR for accidents was borderline increased (SMR 1.95, 95% CI 0.97 to 3.92), with significant heterogeneity between the studies (I^2 73%, p=0.03). The meta-analysis on infections (combined pneumonia, septicaemia, and other infections) showed an increased SMR (SMR 1.66, 95% CI 1.15 to 2.38). Although there was significant heterogeneity in effect size between the studies (I^2 75%, p<0.01), the direction of SMR was the same in most studies. Mortality from suicide was increased for the most part (SMR 3.37, 95% CI 1.52 to 7.50), with significant heterogeneity between the studies (I^2 92%, p<0.01). Despite the heterogeneity in effect sizes, all the studies

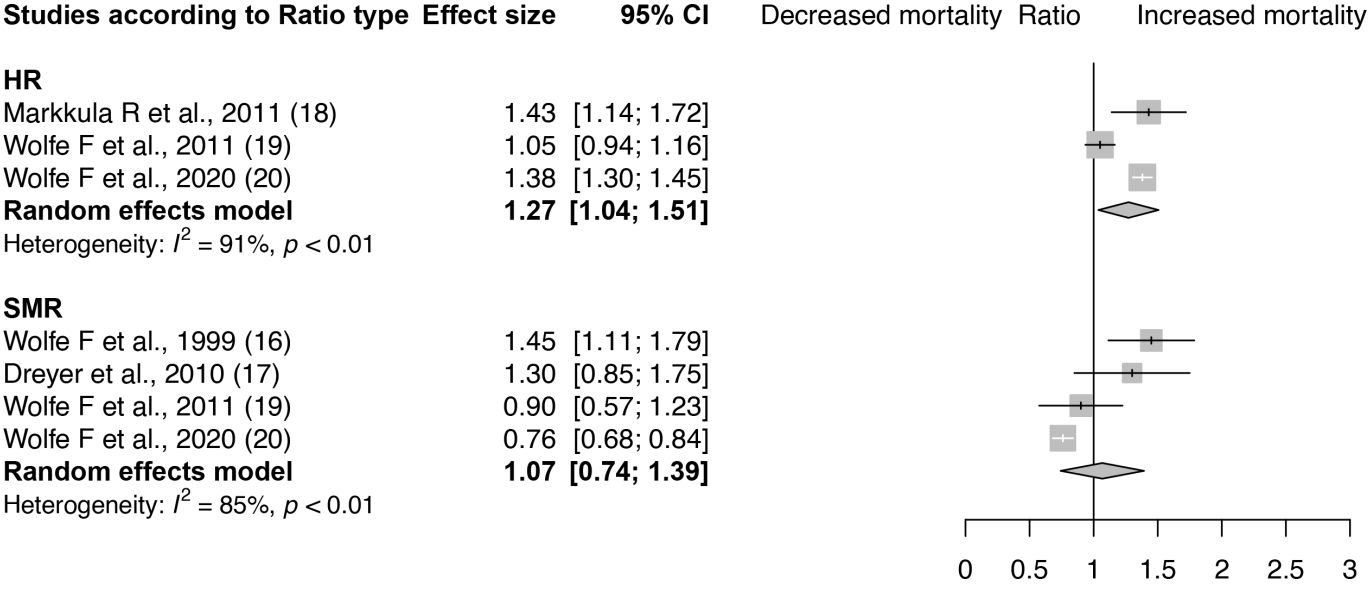

Figure 2 Forest plot on all-cause mortality in fibromyalgia patients. HR, hazard ratio, SMR, standardised mortality ratio.

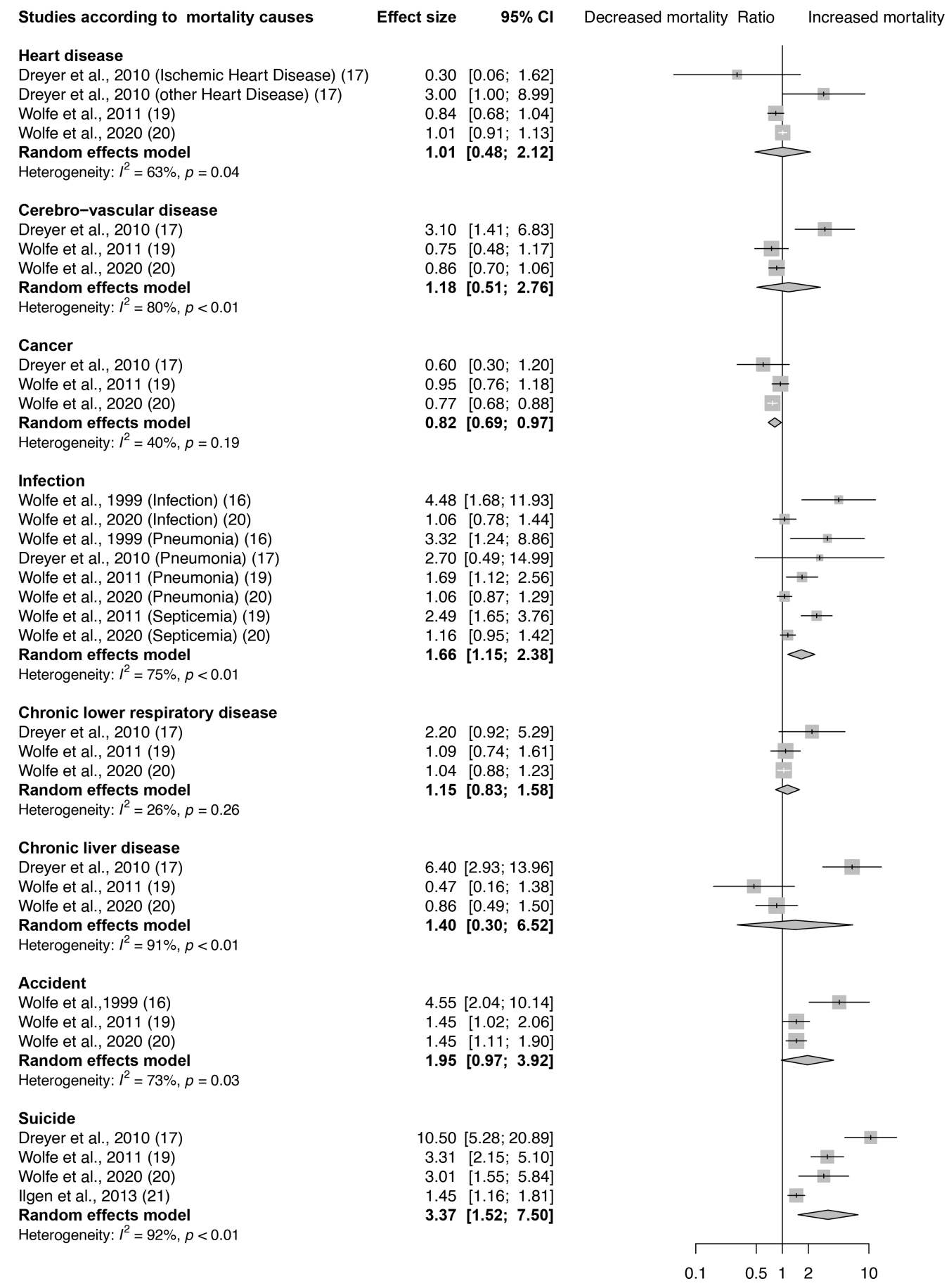

Figure 3 Forest plot of subgroups on different causes of mortality in fibromyalgia patients.

Table 2 Specific-cause mortality in studies not included in meta-analysis

Mortality cause/study	Number of patients	Effect size (95% CI)
Alzheimer's disease		
Wolfe *et al*[19]	8186	0.57 (0.29 to 1.13)*
Wolfe *et al*[20]	9300	0.99 (0.76 to 1.28)*
Parkinson's disease		
Wolfe *et al*[19]	8186	0.22 (0.00 to 1.23)*
Wolfe *et al*[20]	9300	0.57 (0.25 to 1.27)*
Nephritis/nephrotic syndrome/nephrosis		
Wolfe *et al*[19]	8186	0.93 (0.50 to 1.72)*
Wolfe *et al*[20]	9300	0.99 (0.72 to 1.38)*
Essential hypertension/hypertensive renal disease		
Wolfe *et al*[19]	8186	0.95 (0.40 to 2.23)*
Wolfe *et al*[20]	9300	2.12 (1.20 to 3.74)*
Perioperative in-hospital mortality		
Hesler *et al*[22]	89 589	0.81 (0.73 to 0.89)†
Opioid use disorder related in-hospital mortality		
Singh *et al*[23]	5309	0.37 (0.27 to 0.51)

*Standardised mortality ratio.
†Odds ratio

on mortality from suicide showed an increase in SMR, although to different degrees. A decreased mortality rate was seen for cancer (SMR 0.82, 95% CI 0.69 to 0.97), without significant heterogeneity between the studies (I^2 40%, p=0.19).

The following are the results of studies on other causes of mortality, which were not included in the meta-analysis due to the small number of studies (table 2). Two studies examined SMR for Alzheimer's disease, Parkinson's disease, hypertension, and nephritic/nephrotic syndrome. There was no evidence of increased mortality except for one study,[20] which demonstrated increased mortality from hypertension among patients with a fibromyalgia diagnosis based on the 2016 criteria (SMR 2.12, 95% CI 1.20 to 3.74). Two studies that assessed in-hospital perioperative and opioid use disorder related mortality showed a decreased mortality rate with OR 0.81 (95% CI 0.73 to 0.89) and OR 0.37 (95% CI 0.27 to 0.51), respectively.

Outcomes: sensitivity analysis of all-cause mortality, based on studies that used the 1990 criteria for the diagnosis of fibromyalgia only

When the meta-analysis included only studies that used the 1990 diagnostic criteria for fibromyalgia,[16–19] all-cause mortality was not increased among these patients, by either HR or SMR (figure 4).

Risk of study bias

The results of the Newcastle-Ottawa scale for the risk of bias assessment of the included studies are shown in table 3. All of the eight studies were of good quality (7–9/9)

DISCUSSION

This is the first study to address the question of excess mortality among patients with clinical fibromyalgia. There was no increase in SMR for all-cause mortality, but HR was increased significantly by 27%. Thus, the mortality rate for fibromyalgia seems to be increased when the time component is considered, since HR is a better measure of mortality risk over time and all three studies that assessed HR had a long follow-up period, that ranged from 16 to 31 years. Interestingly, the sensitivity analysis of studies that used the 1990 diagnostic criteria showed no increased mortality by either HR or SMR. In his study, Wolfe *et al*[20] also showed that the 2016 criteria explained a larger percentage of variance and had a stronger effect than the 1990 criteria on both SMR

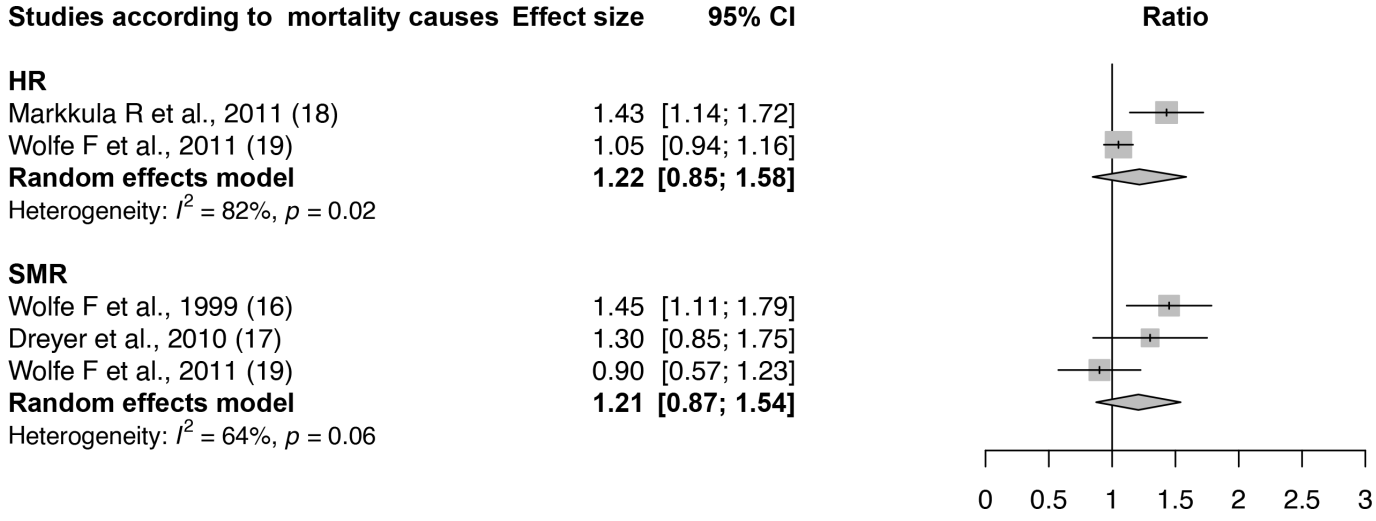

Figure 4 Forest plot for all-cause mortality in fibromyalgia patients, based on the studies that used the 1990 diagnostic criteria. HR, hazard ratio; SMR, standardised mortality ratio.

Table 3 Risk of bias assessment

Study	Selection (max 4 *)			Comparability (max 2 *)		Outcome (max 3 *)			
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts on basis of design or analysis	Assessment of outcome	Sufficient follow-up	Adequate follow-up	Total score
Wolfe *et al*, 1999[16]	*	*	*	*	**	*	*	*	9/9
Dreyer *et al*, 2010[17]	*		*	*	*	*	*	*	7/9
Markkula *et al*, 2011[18]		*	*	*	**	*	*	*	8/9
Wolfe *et al*, 2011[19]	*	*	*	*	**	*	*	*	9/9
Wolfe *et al*, 2020[20]	*	*	*	*	*	*	*	*	9/9
Ilgen *et al*, 2013[21]		*	*	*	**	*		*	7/9
Hesler *et al*, 2014)[22]	*	*	*	*	**	*	*	*	9/9
Singh *et al*, 2021[23]	*	*	*	*		*	*	*	7/9

and RR for all-cause mortality. As the main difference between the 1990 criteria and the later revisions is the lack of recognition of other somatic symptoms, such as sleep disturbance, cognitive symptoms and fatigue, these symptoms would seem to have an impact on mortality. A few meta-analyses that addressed the association between chronic widespread pain with all-cause mortality[11 24 25] reported an increased mortality, either with borderline statistical significance[11 25] or with statistical significance.[24] This increase almost disappeared after adjustment for comorbidity,[25] supporting the hypothesis that it is comorbidity and not chronic pain per se that is associated with increased mortality.

We tried to identify studies that assessed an association between clinical fibromyalgia and mortality rates. Thus, patients in the current cohort had 'tender points' on physical examination (1990 criteria), or suffered from other somatic symptoms that comprise the 'symptom severity scale' (2010, 2011 or 2016 criteria), in addition to chronic widespread pain. So, although the diagnostic criteria for fibromyalgia have evolved over the years,[26] our meta-analysis approaches a real-life situation with a mixed population of patients that were diagnosed over the years by different fibromyalgia criteria.

Due to significant heterogeneity across the studies, which were also small in number, no clear conclusions can be drawn from the available data. However, it is possible that for the subgroup of patients diagnosed by the 1990 criteria there is no increased risk for mortality, and for those diagnosed by later versions the risk is increased. As only minimally adjusted effect measures were extracted from the included studies (age and sex, where possible), our study was not designed to address the question of whether fibromyalgia per se, or its degree of comorbidity, is the reason for this increase. As for specific-cause mortality, an impressive finding is the highly increased SMR for suicide mortality, with all the studies demonstrating an increased risk. A recent systematic review on over 390 000 fibromyalgia patients described a prominently increased suicidal ideation rate and suicide attempts among fibromyalgia patients.[27] The physical and especially the psychiatric comorbidities, that are characteristic of fibromyalgia patients,[6–8] are possible explanations for this finding. The finding of increased mortality associated with accidents can stem from fatigue, unrefreshing sleep, and the concentration difficulties that accompany fibromyalgia, and are a component of its diagnostic criteria since 2010.[26] More and more evidence supports immune system involvement and inflammation in fibromyalgia pathophysiology,[28–30] which can explain the finding of increased mortality from infections. Physical comorbidity may be an additional explanation.[6–8] The results of our meta-analysis point to decreased cancer mortality, without heterogeneity between the studies. Previous meta-analyses, that examined cancer mortality among patients who suffer from chronic widespread pain, showed increased mortality in one study,[11] and no difference in mortality in another.[24] We believe that a logical explanation for the finding of decreased cancer mortality in fibromyalgia patients is extensive utilisation of health services, including imaging tests that can serve as secondary prevention or early detection for these patients.[31 32] Mortality from heart disease was not increased in our study. The results of meta-analyses on the association of chronic pain with heart/cardiovascular mortality varied, with a borderline increase in mortality in one study,[11] no difference in mortality in another,[24] and a significant increase in mortality in the third,[33] although the criteria of pain distribution were different in those studies. Contrary to our finding of no association between fibromyalgia and cerebrovascular mortality, one meta-analysis[33] found an increased mortality rate, but it included participants with chronic, not necessarily widespread, pain. Similar to findings from meta-anlyses on chronic pain,[11 24] in our study fibromyalgia was not associated with increased respiratory mortality. No other meta-analysis assessed an association of widespread pain or fibromyalgia with liver disease and this association was not statistically significant in our meta-analysis. A potential explanation for the interesting finding of decreased in-hospital mortality for perioperative or opioid use disorder is the disproportionate extent of medical surveillance for fibromyalgia patients.

Strengths and limitations

The main strength of our study is the thorough systematic search of the literature to identify all available studies on the subject. All included studies were of good quality and included a large number of patients (188 751). Both all-cause mortality and specific causes of mortality were assessed. The main limitation of our study is different definitions of fibromyalgia that were used in the included studies, most of them including a mixed population of patients who were diagnosed using varying criteria. On the other hand, as mentioned above, this situation approaches a real-life situation with a heterogeneous cohort of fibromyalgia patients in terms of diagnostic criteria. Most studies included patients with both primary and secondary types of fibromyalgia, which could certainly have an impact on mortality. All of the included studies had participants with comorbidities. More than that, unadjusted effect measures were extracted from the included studies. Thus, our study does not address the question of whether fibromyalgia per se, or the degree of comorbidity, is associated with mortality, which is a very important issue. Since comorbidities are probably the link between the fibromyalgia and mortality and causes of death, further studies that address this point are crucial. Although most of the studies on specific-cause mortality used the same risk ratio (SMR), leading to a homogeneous effect measure, one study[21] that assessed suicide mortality used HR. Another limitation is the small number of studies that assessed each cause of mortality. The degree of heterogeneity between the studies was significant for most types of mortality, but when the

number of studies is less than 20, I^2 should be interpreted with caution.[34]

CONCLUSION

To our knowledge, this is the first review designed to assess whether patents with fibromyalgia have an increased mortality rate. The results of the study indicate a possible increase in risk for all-cause mortality and for specific-cause mortality from suicide, infections, and accidents. The cancer mortality rate was decreased and there was a probable decrease in in-hospital mortality during short-term hospitalisations. These possible risks could represent a serious public health problem, given the high prevalence of the condition. Studies have shown that medical staff are reluctant to accept fibromyalgia as a medical condition, and they face emotional and psychological difficulties interacting with these patients and coping with their disorder.[35 36] Fibromyalgia is often called an 'imaginary condition', with ongoing debates on the legitimacy and clinical usefulness of this diagnosis.[37] Our review provides further proof that fibromyalgia patients should be taken seriously, with particular focus on screening for suicidal ideation, prevention of accidents, and prevention and treatment of infections.

Contributors YT-G designed the work, and contributed to the acquisition, analysis and interpretation of data, drafted the work, and approved the final version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. YT-G is responsible for the overall content as the guarantor. RP contributed to the acquisition, analysis and interpretation of data for the work. He revised it critically for important intellectual content; and approved the final version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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REFERENCES

1 Sauch Valmaña G, Miró Catalina Q, Vidal-Alaball J. Prevalence and incidence of patients with fibromyalgia in Catalonia between 2010 and 2017: a descriptive observational study. *J Prim Care Community Health* 2022;13:21501319221094169.
2 Collin SM, Bakken IJ, Nazareth I, *et al*. Trends in the incidence of chronic fatigue syndrome and fibromyalgia in the UK, 2001-2013: a clinical practice research datalink study. *J R Soc Med* 2017;110:231–44.
3 Wolfe F, Smythe HA, Yunus MB, *et al*. American College of Rheumatology 1990 criteria to the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum* 1990;33:160–72.
4 Wolfe F, Clauw DJ, Fitzcharles M-A, *et al*. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016;46:319–29.
5 Galvez-Sánchez CM, Reyes Del Paso GA. Diagnostic criteria for fibromyalgia: critical review and future perspectives. *J Clin Med* 2020;9:1219.
6 Buskila D, Cohen H. Comorbidity of fibromyalgia and psychiatric disorders. *Curr Pain Headache Rep* 2007;11:333–8.
7 Fitzcharles M-A, Perrot S, Häuser W. Comorbid fibromyalgia: a qualitative review of prevalence and importance. *Eur J Pain* 2018;22:1565–76.
8 Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities. *Curr Opin Rheumatol* 2018;30:94–100.
9 Wolfe F, Ablin J, Guymer EK, *et al*. The relation of physical comorbidity and multimorbidity to fibromyalgia, widespread pain, and fibromyalgia-related variables. *J Rheumatol* 2020;47:624–31.
10 Kim Y, Umeda M. Chronic pain, physical activity, and all-cause mortality in the US adults: the NHANES 1999-2004 follow-up study. *Am J Health Promot* 2019;33:1182–6.
11 Macfarlane GJ, Barnish MS, Jones GT. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. *Ann Rheum Dis* 2017;76:1815–22.
12 Boska RL, Bishop TM, Ashrafioun L. Pain conditions and suicide attempts in military veterans: a case-control design. *Pain Med* 2021;22:2846–50.
13 Wells GA, Shea B, O"Connell D, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: to treat or not to treat, that is the question! A systematic review and meta-analysis. 2011.
14 R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, Available: http://www.r-project.org/index.html
15 Harrer M, Cuijpers P, Furukawa TA, *et al*. *Doing meta-analysis in R: a hand-on guide*. Boca Raton: Chapman & Hall/CRC Press, 2021.
16 Wolfe F, Hawley DJ, Anderson J. The long-term outcomes of fibromyalgia: rates and predictors of mortality in fibromyalgia after 25 years follow-up. *Arthritis Rheum* 1999:S395.
17 Dreyer L, Kendall S, Danneskiold-Samsøe B, *et al*. Mortality in a cohort of Danish patients with fibromyalgia: increased frequency of suicide. *Arthritis Rheum* 2010;62:3101–8.
18 Markkula R, Kalso E, Huunan-Seppälä A, *et al*. The burden of symptoms predicts early retirement: a twin cohort study on fibromyalgia-associated symptoms. *Eur J Pain* 2011;15:741–7.
19 Wolfe F, Hassett AL, Walitt B, *et al*. Mortality in fibromyalgia: a study of 8,186 patients over thirty-five years. *Arthritis Care Res* 2011;63:94–101.
20 Wolfe F, Ablin J, Baker JF, *et al*. 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. *Semin Arthritis Rheum* 2020;50:1457–64.
21 Ilgen MA, Kleinberg F, Ignacio RV, *et al*. Noncancer pain conditions and risk of suicide. *JAMA Psychiatry* 2013;70:692–7.
22 Hesler BD, Dalton JE, Singh H, *et al*. Association between fibromyalgia and adverse perioperative outcomes. *Br J Anaesth* 2014;113:792–9.
23 Singh JA, Cleveland JD. Time trends in opioid use disorder hospitalizations in gout, rheumatoid arthritis, fibromyalgia, osteoarthritis, and low back pain. *J Rheumatol* 2021;48:775–84.
24 Smith D, Wilkie R, Uthman O, *et al*. Chronic pain and mortality: a systematic review. *PLoS ONE* 2014;9:e99048.
25 Åsberg AN, Heuch I, Hagen K. The mortality associated with chronic widespread musculoskeletal complaints: a systematic review of the literature. *Musculoskeletal Care* 2017;15:104–13.
26 Wolfe F, Rasker JJ. The evolution of fibromyalgia, its concepts, and criteria. *Cureus* 2021;13:e20010.
27 Adawi M, Chen W, Bragazzi NL, *et al*. Suicidal behavior in fibromyalgia patients: rates and determinants of suicide ideation, risk, suicide, and suicidal attempts - a systematic review of the literature and meta-analysis of over 390,000 fibromyalgia patients. *Front Psychiatry* 2021;12:629417.
28 Fineschi S, Klar J, Gustafsson KA, *et al*. Inflammation and interferon signatures in peripheral B-lymphocytes and sera of individuals with fibromyalgia. *Front Immunol* 2022;13:874490.
29 Erbacher C, Vaknine S, Moshitzky G, *et al*. Distinct cholinomir blood cell signature as a potential modulator of the cholinergic system in women with fibromyalgia syndrome. *Cells* 2022;11:1276.

30 Khamisy-Farah R, Fund E, Raibman-Spector S, *et al*. Inflammatory markers in the diagnosis of Fibromyalgia. *Isr Med Assoc J* 2021;23:801–4. Available: https://www-ima-org-il.ezproxy.bgu.ac.il/MedicineIMAJ/viewarticle.aspx?year=2021&month=12&page=801
31 Margolis JM, Masters ET, Cappelleri JC, *et al*. Evaluating increased resource use in fibromyalgia using electronic health records. *Clinicoecon Outcomes Res* 2016;8:675–83.
32 Silverman S, Dukes EM, Johnston SS, *et al*. The economic burden of fibromyalgia: comparative analysis with rheumatoid arthritis. *Curr Med Res Opin* 2009;25:829–40.
33 Fayaz A, Ayis S, Panesar SS, *et al*. Assessing the relationship between chronic pain and cardiovascular disease: a systematic review and meta-analysis. *Scand J Pain* 2016;13:76–90.
34 Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al*. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006;11:193–206.
35 Briones-Vozmediano E. The social construction of fibromyalgia as a health problem from the perspective of policies, professionals, and patients. *Glob Health Action* 2017;10:1275191.
36 Aloush V, Niv D, Ablin JN, *et al*. Good pain, bad pain: illness perception and physician attitudes towards rheumatoid arthritis and fibromyalgia patients. *Clin Exp Rheumatol* 2021;39:54–60.
37 Häuser W, Fitzcharles M-A. Facts and myths pertaining to fibromyalgia. *Dialogues Clin Neurosci* 2018;20:53–62.