View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Repositori d'Objectes Digitals per a l'Ensenyament la Recerca i la Cultura

*Age and Ageing* 2018; **0:** 1–6
doi: 10.1093/ageing/afy163

© The Author(s) 2018. Published by Oxford University Press on behalf of the British Geriatrics Society. All rights reserved. For permissions, please email: journals.permissions@oup.com

# Frequency, intensity and localization of pain as risk factors for frailty in older adults

Isabel Rodríguez-Sánchez[1,2†], Esther García-Esquinas[1,3†], Arthur E. Mesas[4], José María Martín-Moreno[5], Leocadio Rodríguez-Mañas[6], Fernando Rodríguez-Artalejo[1,3,7]

[1]Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid/IdiPaz, Madrid, Spain
[2]Department of Geriatric Medicine, Hospital Universitario La Paz/IdiPaz, Madrid, Spain
[3]CIBERESP (CIBER of Epidemiology and Public Health), Madrid, Spain
[4]Department of Public Health, Universidade Estadual de Londrina, Londrina, Brazil
[5]Preventive Medicine and Public Health and University Clinical Hospital INCLIVA, University of Valencia, Valencia, Spain
[6]Department of Geriatric Medicine, Hospital Universitario de Getafe and CIBERFES (CIBER of Frailty and Healthy Ageing), Getafe, Spain
[7]IMDEA-Food Institute, CEI UAM+CSIC, Madrid, Spain

Address correspondence to: Esther García-Esquinas, MD, Department of Preventive Medicine and Public Health., School of Medicine., Universidad Autónoma de Madrid. Calle del Arzobispo Morcillo 4, 28029 Madrid, Spain. Tel: (+34) 91-497-27-61, Fax: (+34) 91-497-53-53, Email: esthergge@gmail.com
[†]Both authors have contributed equally to this manuscript.

## Abstract

**Background:** the association between pain characteristics and frailty risk is uncertain.
**Objective:** to investigate the separate impact of the frequency, intensity and location of pain on frailty risk and its possible mechanisms.
**Methods:** prospective cohort of 1505 individuals ≥63 years followed between 2012 and 2015 in Spain. In 2012, pain was classified into: lowest pain (Score 0), middle pain (Score 1–4) and highest pain (Score 5–6). Incident frailty was assessed in 2015 as having ≥3 Fried criteria or a Frailty Index (FI) ≥0.30.
**Results:** in multivariate analyses, the risk of frailty (measured with the Fried criteria or the FI) increased progressively with the frequency of pain, its intensity and the number of pain locations. Compared with those having the lowest pain score, the odds ratio (95% confidence interval) of Fried-based frailty was 1.24 (0.56–2.75) in the middle score and 2.39 (1.34–4.27; *P*-trend <0.01) in the highest score. Corresponding values for frailty as FI ≥0.30 were 1.39 (0.80–2.42) and 2.77 (1.81–4.24; *P*-trend <0.01). Odds ratios did not change after adjustment for alcohol intake, Mediterranean diet adherence or sedentary time, but were reduced with adjustment for pain-associated chronic diseases (cardiovascular disease, diabetes, chronic lung disease, osteomuscular disease and depression). A higher pain score was linked to higher risk of exhaustion and low physical activity (two out of five Fried criteria) and to a worse score in all FI domains.
**Conclusion:** frequency, intensity and location of pain were associated with higher risk of frailty. Study associations were partly explained by pain-associated morbidity.

**Keywords:** *pain, frailty, functional impairment, older people, prospective*

## Introduction

Persistent pain is a frequent health problem in older adults. In the English Longitudinal Study of Ageing (ELSA), conducted on a representative sample of people aged ≥50 years in the UK, 18.1% and 6.6% reported suffering moderate and severe persistent pain, respectively [1]. Also, among 22,280 individuals aged ≥50 years from the 2011 *Survey of Health, Ageing and Retirement Study in Europe*, 57% reported suffering pain in the joints for at least six months prior to the interview [2].

Frailty is a common geriatric syndrome, which is characterized by reduced physiological reserve and increased vulnerability to even minors stressors (e.g. infection, a new



Downloaded from https://academic.oup.com/ageing/advance-article-abstract/doi/10.1093/ageing/afy163/5126787 by University of New England user on 12 October 2018

drug treatment), which leads to greater risk of adverse outcomes, including falls, hospitalization, disability, institutionalization or death [3, 4]. The frailty syndrome is habitually ascertained using either a phenotypic approach-based on the aggregation of several frailty criteria (e.g. the Fried criteria)-, or the frailty index (FI)-based on the number of health deficits accumulated over time [5]. Although the prevalence of frailty varies with the diagnostic approach, in European populations it is about 10% in those aged ≥60 years [6].

Interestingly, the frequency of both pain and frailty increases with age, and they often coexist. Because of this, and the fact that pain is also a risk factor for falls, functional limitation and death [7, 8], persistent pain has been considered a cause, a consequence, or even an additional manifestation of the frailty phenotype [9].

However, epidemiological evidence on the role of pain as a causal risk factor for frailty is limited. Only a few cross-sectional [10–14] and prospective [1, 15–17] studies have assessed this association. Moreover, no previous study has examined the association between pain and risk of frailty, assessed with both the Fried criteria and the FI. Also, none has evaluated the separate impact of the frequency, intensity and localization of pain on frailty risk, and the mechanisms of this association are still poorly understood. Although it has been suggested that pain may lead to greater sedentariness and worse nutrition which could lead to frailty [1, 18], and although comorbidity in patients with pain may account for pain-associated frailty, we are not aware of any study that has systematically assessed the role of these potential mechanisms.

Therefore, we used data from a cohort of older adults in Spain to examine the prospective association of frequency, intensity and number of localizations of pain with risk of frailty, assessed with both the Fried criteria and the FI. Additionally, we investigated if sedentary behavior, diet quality and morbidity could explain the study associations.

## Methods

### Study design and participants

Data were taken from the Seniors ENRICA, a population-based cohort of Spanish community-dwelling individuals aged ≥60 years recruited in 2008–2010 [19, 20]. Data were collected by telephone interviews and in subsequent home visits that included a face-to-face interview, a physical examination, a diet history, and collection of biological samples. Information was updated in 2012 (Wave 1) and 2015 (Wave 2). Given that information on pain was first obtained in 2012, analyses for this paper were conducted with the 1,821 participants in 2012 who were followed up to 2015. From these individuals, we excluded those with frailty at baseline or incomplete data on frailty at baseline and follow-up; thus, analyses using incident Fried-based frailty were performed with 1,308 individuals, and analyses using incident FI-based frailty with 1,505 people.

Study participants gave informed written consent. The study was approved by the Ethics Research Committee of *La Paz* University Hospital in Madrid.

### Study variables

#### *Pain*

Information on pain was self-reported using 10 questions from the instrument used in the Survey on Chronic Pain in Europe [21]. Individuals with pain at least ≥2 times/week in the last 6 months were deemed to suffer persistent pain; those with pain 1 time/week, 1–3 times/month or <1 time/month were considered to have sporadic pain; and those with no pain in the last 6 months were classified as having no pain. Pain intensity was assessed according to its impact on habitual activities; individuals whose pain troubled them moderately, a lot or completely were classified as suffering moderate-high-intensity pain; those with little trouble as light-intensity pain; and those with no trouble as very low intensity pain. Participants classified as with high-intensity, light and very low-intensity pain reported an average intensity of 7.93, 5.05 and 2.59 points (in a scale from 1 [no pain] through 10 [a pain I cannot even imagine bearing]), respectively. Pain location was reported in six categories: (a) head and neck; (b) back; (c) bones and joints; (d) legs; (e) arms and (f) other sites; this served to classify individuals with pain according to the number of pain sites: 0, 1–2 and ≥3.

A pain scale including frequency, intensity and number of pain sites was built. Sporadic and frequent pain were assigned a score of 1 and 2, respectively; light and moderate-high intensity a score of 1 and 2, respectively; and 1–2 and ≥3 sites a score of 1 and 2, respectively. The scale ranged from 0 to 6 (worse pain), and classified participants into three groups: lowest (score 0), middle (score 1–4) and highest score (score 5–6). The cut-off point between middle and highest pain was the median score in those with pain score 1 through 6.

#### *Frailty*

According to the criteria proposed by Fried *et al.* in the Cardiovascular Health Study (CHS) [22], individuals meeting ≥3 of five phenotypic criteria were considered as frail (see Supplementary Table 1, available at *Age and Ageing* online).

Frailty was also measured with a FI based on 51 items (see Supplementary Table 2, available at *Age and Ageing* online) [23]. Frailty was defined as an FI ≥0.30 [1, 15, 24]. In our cohort, the hazard ratio for 5-year mortality of having an FI ≥0.30 vs. <0.30 was 1.50 (95% confidence interval CI: 1.09–2.06).

#### *Other variables*

At baseline, data on age, sex, education, tobacco smoking, measured BMI [25], adherence to the Mediterranean diet (MD) as per the MEDAS index (excluding alcohol intake)



Downloaded from https://academic.oup.com/ageing/advance-article-abstract/doi/10.1093/ageing/afy163/5126787 by University of New England user on 12 October 2018

[26] and sedentary behavior (h/day watching TV) [27] were collected. Participants reported whether they had any of the following physician-diagnosed diseases: cardiovascular disease (ischemic heart disease, stroke, heart failure), diabetes, chronic lung disease (asthma, chronic bronchitis), osteomuscular disease (osteoarthritis, arthritis or hip fracture) and depression requiring treatment.

### Statistical analyses

Among individuals free of frailty at baseline, the association of sporadic and persistent pain in 2012 with the risk of frailty up to 2015 was summarized with odds ratios (OR) and their 95% CI, obtained from logistic regression. The 'no pain' category was used as reference in the analyses. A dose–response association was estimated by modeling the pain frequency categories as a continuous variable. Five models were fitted. Model 1 adjusted for age, sex, education, tobacco smoking and BMI. Next, the potential mediation of alcohol intake, TV watching and adherence to the MD to the associations between pain and frailty risk was assessed by adding each of these variables separately to model 1 (Models 2–4). Then, a full model adjusting simultaneously for all covariates was fitted (Model 5). In analyses using the Fried criteria, a sixth model adjusting for the studied covariates and for the number of chronic diseases was estimated. Similar analyses were performed using pain intensity (very low [reference], light and moderate-high), number of pain locations (0 [reference], 1–2, ≥3 sites), and pain scale (lowest [reference], middle and highest score) as exposure variables. Analyses based on Models 1 and 5 were replicated for each Fried criterion (among individuals free of that criterion at baseline) and for each dimension of FI (among individuals with a score <0.30 in that dimension at baseline).

Multivariate linear regression models were used to assess the association between pain in 2012 and worsening frailty, according to FI, from 2012 to 2015. Regression analyses were adjusted as above and additionally adjusted for FI in 2012. Results were expressed as beta coefficients (95%CI) of the FI score.

## Results

### Characteristics of study participants

Among study participants at baseline, 12.6% reported sporadic pain and 31.3% persistent pain. Corresponding figures were 17.7 and 26.1% for light and moderate-high-intensity pain, and 22.7 and 20% for pain in 1–2 sites and ≥3 sites, respectively. see Supplementary Tables 3 and 4, available at *Age and Ageing* online show the sociodemographic, lifestyle and clinical variables of study participants according to pain characteristics. During follow-up, 67 individuals developed frailty based on Fried criteria and 141 based on FI.

### Pain status and frailty as per the fried criteria

Table 1 shows that, compared to people with no pain, those with more frequent pain were more likely to become frail (Model 1, OR:1.9, 95%CI:1.1–3.4; *P*-trend = 0.03). Results were in the same direction for pain intensity (OR moderate-high vs. very low intensity 2.4, 95%CI: 1.4–4.3; *P*-trend <0.01) and for the number of pain sites (OR ≥ 3 vs. 0 sites:2.5, 95% CI: 1.4–4.6; *P*-trend <0.01). Accordingly, the pain scale showed a positive dose–response with frailty risk: OR middle vs. lowest score: 1.2, 95%CI: 0.6–2.8; OR highest vs. lowest score: 2.4, 95%CI: 1.3–4.3; *P*-trend <0.01. Additional adjustment for alcohol intake, sedentary time or MEDAS index did not materially change the results (Models 2–5). Further adjustment for chronic diseases (Model 6) somewhat reduced the associations: the OR for the highest vs. lowest score was 2.5 in Model 5 and 1.9 in Model 6. Results in Model 5 were not modified by sociodemographic and lifestyle variables or chronic diseases (*P* for interaction >0.05 in all cases).

A higher frequency, intensity and number of locations of pain, as well as a higher score on the pain scale, were associated with higher risk of exhaustion and low physical activity. Results for low gait speed and muscle weakness were in the same direction, although they did not reach statistical significance. Weight loss did not show any association (see Supplementary Table 6, available at *Age and Ageing* online).

### Pain status and frailty as per the frailty index

Table 2 shows that the risk of FI ≥0.30 increased progressively with the frequency of pain, its intensity and the number of pain locations (model 1). As a result, compared with the lowest score on the pain scale, the OR of frailty was 1.4 (95%CI: 0.8–2.4) for a middle score and 2.8 (95%CI: 1.8–4.2) for the highest (*P*-trend: <0.01). Results remained similar after further adjustment for alcohol intake, sedentary time and MEDAS index. A higher frequency, intensity and number of locations of pain, and a progressively higher score on the pain scale were consistently associated with a score ≥0.30 on the dimensions of functional impairment, self-rated health and vitality, mental health, and morbidities and health services use (see Supplementary Table 7, available at *Age and Ageing* online). No significant interaction was found with sociodemographic and lifestyle variables or chronic diseases. Results for worsening frailty over the follow-up were in line with those obtained for FI ≥0.30 (see Supplementary Tables 5 and 8, available at *Age and Ageing* online).

## Discussion

In this prospective study of community-dwelling older adults in Spain, the frequency, intensity and location of pain were associated with a higher risk of frailty and most of its components. The study associations were partly explained by pain-associated morbidity.

Our results are in line with previous prospective studies. The first one, conducted among 2,736 men aged 40–79 years in the European Male Ageing Study, found an association between chronic widespread pain and increased risk of frailty and worsening frailty, as measured with the FI



Downloaded from https://academic.oup.com/ageing/advance-article-abstract/doi/10.1093/ageing/afy163/5126787 by University of New England user on 12 October 2018

**Table 1.** Association between pain status at baseline and risk of frailty (as per Fried criteria) after three years of follow-up ($n$ = 1308).

| | Frailty cases/total | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) | Model 4 OR (95% CI) | Model 5 OR 95% (CI) | Model 6 OR 95% (CI) |
|---|---|---|---|---|---|---|---|
| Frequency of pain | | | | | | | |
| No pain | 27/734 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Sporadic pain | 11/165 | 2.0 (0.9–4.3) | 1.9 (0.9–4.2) | 2.0 (0.9–4.3) | 2.0 (0.9–4.3) | 2.0 (0.9–4.3) | 2.1 (0.9–4.6) |
| Persistent pain | 29/409 | 1.9 (1.1–3.4) | 1.9 (1.1–3.4) | 2.0 (1.1–3.6) | 2.0 (1.1–3.5) | 2.0 (1.1–3.7) | 1.6 (0.9–3.0) |
| *P for trend* | | 0.03 | 0.03 | 0.02 | 0.02 | 0.02 | 0.14 |
| Intensity of pain | | | | | | | |
| Very low | 27/734 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Light | 9/232 | 1.2 (0.6–2.7) | 1.3 (0.6–2.9) | 1.3 (0.6–2.9) | 1.3 (0.5–2.8) | 1.4 (0.6–3.2) | 1.3 (0.6–3.0) |
| Moderate-High | 31/342 | 2.4 (1.4–4.3) | 2.3 (1.3–4.0) | 2.5 (1.4–4.4) | 2.42 (1.4–4.3) | 2.4 (1.3–4.2) | 1.9 (1.0–3.6) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | 0.04 |
| Locations of pain | | | | | | | |
| 0 pain sites | 28/750 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 1–2 pain sites | 14/297 | 1.4 (0.7–2.8) | 1.4 (0.7–2.8) | 1.4 (0.7–2.8) | 1.4 (0.7–2.7) | 1.5 (0.7–2.9) | 1.4 (0.7–2.9) |
| ≥ 3 pain sites | 25/261 | 2.5 (1.4–4.6) | 2.3 (1.3–4.4) | 2.6 (1.4–4.9) | 2.6 (1.4–4.8) | 2.6 (1.4–4.8) | 1.9 (0.9–3.7) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | 0.06 |
| Pain scale | | | | | | | |
| Lowest score | 27/734 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Middle score | 9/223 | 1.2 (0.6–2.8) | 1.3 (0.6–2.8) | 1.3 (0.6–2.9) | 1.3 (0.6–2.8) | 1.3 (0.6–3.0) | 1.4 (0.6–3.1) |
| Highest score | 31/351 | 2.4 (1.3–4.3) | 2.3 (1.3–4.1) | 2.5 (1.4–4.5) | 2.4 (1.4–4.3) | 2.5 (1.4–4.5) | 1.9 (1.0–3.5) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | 0.05 |

OR, Odds Ratio; CI, Confidence interval.

Pain scale: 0 lowest score, 1–4 middle score, 5–6 highest score.

Model 1: Adjusted for sex, age, educational level (≤ primary, secondary, university), tobacco smoking (never-, former, current-smoker) and BMI (<25, 25–29.9, ≥30 kg/m$^2$),

Model 2: As Model 1 and additionally adjusted for alcohol intake (tertiles, g/d).

Model 3: As Model 1 and additionally adjusted for time watching TV (tertiles, h/week).

Model 4: As Model 1 and additionally adjusted for the MEDAS Index (tertiles).

Model 5: As Model 1 and additionally adjusted for alcohol intake (tertiles, g/d), time watching TV (tertiles, h/week) and the MEDAS Index (tertiles).

Model 6: As Model 5 and additionally adjusted for the number of chronic diseases (cardiovascular disease, diabetes, chronic lung disease, osteomuscular disease and depression).

[15]. The same authors, using data from ELSA, subsequently reported that in men and women ≥49 years, moderate and severe pain were linked to greater risk and intensity of FI-based frailty [1]. The third study was conducted among 1,775 older men and women with osteoarthritis (OA), enrolled in the Progetto Veneto Anziani and followed during 4.4 years; lower limb OA-related pain was associated with Fried-based frailty [16]. Finally, among 3,053 US non-frail men and women from the Osteoarthritis Initiative aged 45–79 years, knee pain (particularly bilateral knee pain) was linked to a greater risk of prefrailty and frailty over six years [17].

This present work is unique by showing that each main characteristic of pain has a separate association with frailty; even sporadic pain (presumably of sufficient intensity) and pain of only light-intensity are linked to increased frailty risk. About 13% of participants in our study had sporadic pain, 82.9% had visited a doctor for pain management, and 75% of the latter were prescribed analgesic treatment; corresponding values for light-intensity pain were 16.5, 79.1 and 76.9%. Thus, there is substantial unmet need of treatment for the less severe forms of pain, which may turn into increased frailty risk and its adverse outcomes. Our study is also unique by showing that more severe pain is associated with both the phenotypic- and FI-based frailty. Given that the Fried criteria and many of the FI domains are unrelated, the robustness of the results suggests that there are different mechanisms linking pain and frailty. Given the multidimensional nature of pain, it may affect several biological systems leading to reduced physiological reserve and less ability to maintain homeostasis after exposure to even minor stressors, which are the hallmarks of frailty [12].

Chronic morbidity explained part of the association between pain and frailty based on Fried criteria. Other prospective studies have found that lower limb OA-related pain as well as knee pain, the most common symptom of knee OA, predict phenotypic frailty [16, 17]. Also, in one cross-sectional study with older adults in China the association of pain with frailty was partially mediated by depression, and comorbid depression and pain had an additive interaction on physical frailty [14].

Lastly, previous studies have shown that pain is associated with disability [7], worse health-related quality of life [18], and cognitive impairment [28]. These results are in line with ours because these variables broadly correspond to several domains of the FI.

This study has several limitations. First, the follow-up was 3 years and cannot rule out some reverse causation [8].



Downloaded from https://academic.oup.com/ageing/advance-article-abstract/doi/10.1093/ageing/afy163/5126787 by University of New England user on 12 October 2018

**Table 2.** Association between pain status at baseline and risk of frailty (as per frailty index ≥0.30) after three years of follow-up ($n$ = 1505).

| | Frailty cases/total | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) | Model 4 OR (95% CI) | Model 5 OR 95% (CI) |
|---|---|---|---|---|---|---|
| Frequency of pain | | | | | | |
| No pain | 60/914 | Ref. | Ref. | Ref. | Ref. | Ref. |
| Sporadic pain | 17/172 | 1.7 (0.9–3.0) | 1.7 (1.0–3.1) | 1.6 (0.9–2.9) | 1.7 (1.0–3.1) | 1.7 (1.0–3.1) |
| Persistent pain | 55/391 | 2.4 (1.6–3.6) | 2.4 (1.6–3.7) | 2.4 (1.6–3.6) | 2.5 (1.6–3.7) | 2.4 (1.6–3.7) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| Intensity of pain | | | | | | |
| Very low | 60/914 | Ref. | Ref. | Ref. | Ref. | Ref. |
| Light | 24/254 | 1.7 (1.0–2.8) | 1.8 (1.1–3.0) | 1.7 (1.0–2.9) | 1.8 (1.1–3.0) | 1.8 (1.1–3.1) |
| Moderate-High | 48/309 | 2.5 (1.7–3.9) | 2.5 (1.6–3.9) | 2.4 (1.6–3.8) | 2.6 (1.7–4.0) | 2.5 (1.6–3.8) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| Locations of pain | | | | | | |
| 0 pain sites | 61/930 | Ref. | Ref. | Ref. | Ref. | Ref. |
| 1–2 pain sites | 32/320 | 1.7 (1.1–2.7) | 1.7 (1.1–2.7) | 1.7 (1.0–2.7) | 1.7 (1.1–2.8) | 1.7 (1.1–2.7) |
| ≥3 pain sites | 39/227 | 3.0 (1.9–4.8) | 3.0 (1.9–4.8) | 2.9 (1.8–4.7) | 3.1 (1.9–5.0) | 3.1 (1.9–5.0) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| Pain scale | | | | | | |
| Lowest score | 60/914 | Ref. | Ref. | Ref. | Ref. | Ref. |
| Middle score | 19/240 | 1.4 (0.8–2.4) | 1.4 (0.8–2.5) | 1.4 (0.8–2.4) | 1.4 (0.8–2.5) | 1.5 (0.9–2.6) |
| Highest score | 53/323 | 2.8 (1.8–4.2) | 2.8 (1.8–4.2) | 2.7 (1.8–4.1) | 2.8 (1.9–4.3) | 2.7 (1.8–4.2) |
| *P for trend* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |

OR, Odds Ratio; CI, Confidence interval.

Pain scale: 0 lowest score, 1–4 middle score, 5–6 highest score.

Model 1: Adjusted for sex, age, educational level (≤ primary, secondary, university), tobacco smoking (never-, former, current-smoker) and BMI (<25, 25–29.9, ≥30 kg/m$^2$).

Model 2: As Model 1 and additionally adjusted for alcohol intake (tertiles, g/d).

Model 3: As Model 1 and additionally adjusted for time watching TV (tertiles, h/week).

Model 4: As Model 1 and additional adjusted for the MEDAS Index (tertiles).

Model 5: As Model 1 and additionally adjusted for alcohol intake (tertiles, g/d), time watching TV (tertiles, h/week) and the MEDAS Index (tertiles).

However, the fact that pain predicted low physical activity in those without such criterion at baseline, and that pain increased the score in all components of the FI after adjustment for baseline FI, suggests that reverse causation is not likely to completely explain the study association. Second, the pain questionnaire has not been validated, and we did not collect information on the type of pain (e.g. neuropathic, nociceptive) and its etiology. However, we employed similar items to other widely used questionnaires, and the distribution of pain categories across socio-demographics, lifestyle and chronic diseases was consistent with the literature [29, 30]. Lastly, there was a small number of frailty events, particularly Fried-based cases, in some categories of pain, which led to relatively wide confidence intervals for the study associations; also, morbidity was self-reported and it may underestimate the presence of disease, particularly in their milder forms.

In conclusion, this research shows a dose–response relationship between separate pain characteristics and frailty, assessed with both Fried criteria and FI, in older men and women. Our results are of clinical importance because they show a substantial unmet need of treatment for the less severe forms of pain, which may turn into increased frailty risk. Future research should establish if effective pain management, especially within the context of chronic diseases, could reduce frailty risk.

## Key points

- Among older people, pain is a risk factor for falls, functional limitation and death.
- In this cohort, the prevalence of moderate-high-intensity pain was 26.1%.
- In older people, frequency, intensity and location of pain show a separate dose–response relationship with risk of frailty.
- This relationship is partly explained by pain-associated morbidity.
- Effective chronic pain management, especially within the context of chronic diseases, could reduce frailty risk.

## Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

## Funding

This work was supported by FIS grants 12/1166 and 16/609 (Instituto de Salud Carlos III, State Secretary of R + D + I,



Downloaded from https://academic.oup.com/ageing/advance-article-abstract/doi/10.1093/ageing/afy163/5126787 by University of New England user on 12 October 2018

and FEDER/FSE); the FRAILOMIC Initiative (FP7-HEALTH-2012-Proposal no. 305483-2); the ATHLOS project (EU H2020-Project ID: 635316); and funding from the CIBERESP (Instituto de Salud Carlos III, State Secretary of R + D + I, and FEDER/FSE).

## Conflicts of interest

None.

## References

1. Wade KF, Marshall A, Vanhoutte B, Wu FC, O'Neill TW, Lee DM. Does pain predict frailty in older men and women? Findings From the English Longitudinal Study of Ageing (ELSA). J Gerontol A Biol Sci Med Sci 2017; 72: 403–9.
2. Calvó-Perxas L, Vilalta-Franch J, Turró-Garriga O, López-Pousa S, Garre-Olmo J. Gender differences in depression and pain: a two year follow-up study of the Survey of Health, Ageing and Retirement in Europe. J Affect Disord 2016; 193: 157–64.
3. Morley JE, Vellas B, van Kan GA *et al*. Frailty consensus: a call to action. J Am Med Dir Assoc 2013; 14: 392–7.
4. Rodríguez-Mañas L, Féart C, Mann G *et al*. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci 2013; 68: 62–7.
5. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752–62.
6. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012; 60: 1487–92.
7. Andrews JS, Cenzer IS, Yelin E, Covinsky KE. Pain as a risk factor for disability or death. J Am Geriatr Soc 2013; 61: 583–9.
8. Stubbs B, Schofield P, Binnekade T, Patchay S, Sepehry A, Eggermont L. Pain is associated with recurrent falls in community-dwelling older adults: evidence from a systematic review and meta-analysis. Pain Med 2014; 15: 1115–28.
9. Lohman MC, Whiteman KL, Greenberg RL, Bruce ML. Incorporating persistent pain in phenotypic frailty measurement and prediction of adverse health outcomes. J Gerontol A Biol Sci Med Sci 2017; 72: 216–22.
10. Blyth FM, Rochat S, Cumming RG *et al*. Pain, frailty and comorbidity on older men: the CHAMP study. Pain 2008; 140: 224–30.
11. Coyle PC, Sions JM, Velasco T, Hicks GE. Older adults with chronic low back pain: a clinical population vulnerable to frailty? J Frailty Aging 2015; 4: 188–90.
12. Shega JW, Dale W, Andrew M, Paice J, Rockwood K, Weiner DK. Persistent pain and frailty: a case for homeostenosis. J Am Geriatr Soc 2012; 60: 113–7.
13. Coelho T, Paúl C, Gobbens RJJ, Fernandes L. Multidimensional frailty and pain in community dwelling elderly. Pain Med 2017; 18: 693–70.
14. Tian X, Wang C, Qiao X *et al*. The association between pain and frailty among Chinese community-dwelling older adults: depression as a mediator and its interaction with pain. Pain 2017. doi:10.1097/j.pain.0000000000001105; [Epub ahead of print].
15. Wade KF, Lee DM, McBeth J *et al*. Chronic widespread pain is associated with worsening frailty in European men. Age Ageing 2016; 45: 268–74.
16. Veronese N, Maggi S, Trevisan C *et al*. Pain Increases the Risk of Developing Frailty in Older Adults with Osteoarthritis. Pain Med 2017; 18: 414–27.
17. Bindawas SM, Vennu V, Stubbs B. Longitudinal Relationship Between Knee Pain Status and Incident Frailty: Data from the Osteoarthritis Initiative. Pain Med 2017. doi:10.1093/pm/pnx296; [Epub ahead of print].
18. Stubbs B, Schofield P, Patchay S. Mobility Limitations and Fall-Related Factors Contribute to the Reduced Health-Related Quality of Life in Older Adults With Chronic Musculoskeletal Pain. Pain Pract 2016; 16: 80–9.
19. Hernández-Aceituno A, Pérez-Tasigchana RF. Guallar-Castillón P1, López-García E, Rodríguez-Artalejo F, Banegas JR. Combined Healthy Behaviors and Healthcare Services Use in Older Adults. Am J Prev Med 2017; 53: 872–81.
20. García-Esquinas E, Andrade E, Martínez-Gómez D, Caballero FF, López-García E, Rodríguez-Artalejo F. Television viewing time as a risk factor for frailty and functional limitations in older adults: results from 2 European prospective cohorts. Int J Behav Nutr Phys Act 2017; 14: 54.
21. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006; 10: 287–333.
22. Fried LP, Tangen CM, Walston J *et al*. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–56.
23. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008; 8: 24.
24. García-García FJ, Carcaillon L, Fernandez-Tresguerres J *et al*. A new operational definition of frailty: the Frailty Trait Scale. J Am Med Dir Assoc 2014; 15: 371.e7–371.e13.
25. Gutiérrez-Fisac JL, Guallar-Castillón P, León-Muñoz LM, Graciani A, Banegas JR, Rodríguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008-2010: the ENRICA study. Obes Rev 2012; 13: 388–92.
26. Guallar-Castillon P, Sagardui-Villamor J, Balboa-Castillo T *et al*. Validity and reproducibility of a Spanish dietary history. PLoS One 2014; 9: e86074.
27. Martinez-Gonzalez MA, Lopez-Fontana C, Varo JJ, Sanchez-Villegas A, Martinez JA. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study. Public Health Nutr 2005; 8: 920–7.
28. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Prog Neurobiol 2011; 93: 385–404.
29. Miró J, Paredes S, Rull M *et al*. Pain in older adults: a prevalence study in the Mediterranean region of Catalonia. Eur J Pain 2007; 11: 83–92.
30. Thiem U, Lamsfuß R, Günther S *et al*. Prevalence of self-reported pain, joint complaints and knee or hip complaints in adults aged ≥ 40 years: a cross-sectional survey in Herne, Germany. PLoS One 2013; 8: e60753.

**Received 2 July 2018; editorial decision 11 September 2018**

Downloaded from https://academic.oup.com/ageing/advance-article-abstract/doi/10.1093/ageing/afy163/5126787 by University of New England user on 12 October 2018