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Version: Accepted Version

Article:
Brown, L, Young, JB, Clegg, A et al. (2015) Pain in older people with frailty. Reviews in Clinical Gerontology, 25 (3). pp. 159-171. ISSN: 0959-2598

https://doi.org/10.1017/S0959259815000143

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Title: Pain in older people with frailty

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Word count (excluding references and table) 3,562

Summary and Key words (100-150 words)

In this review we identified cohort and cross-sectional studies which assessed pain in community-dwelling older people (> 65 years) reliably characterised as frail. Secondly, we considered biologically plausible mechanisms which may alter pain perception, or contribute to, or exacerbate pain in an older person with frailty. Thirdly, we considered specific implications of pain management for this group of people. From the limited data from the seven included studies, it would appear that the presence of pain is higher in older people with frailty compared to people characterised as pre-frail or not frail. Thus, older people reporting pain are more likely to be frail. However, a lack of prospective data precludes inferences about the direction of the relationship: that is whether pain or frailty is the antecedent. Further research is needed to understand the direction of the relationship, and to identify appropriate pain management strategies for older people with frailty.

Key words: older people, frailty, pain, analgesia

Introduction

Many chronic conditions such as osteoarthritis, osteoporosis, post-herpetic neuralgia, cancer and comorbidities are associated with both nociceptive and neuropathic pain, and become more prevalent with age [1, 2]. Pain is therefore common amongst older people, with prevalence rates of persistent pain in older adults in the community at over 40% [3].

Frailty is a disorder of several inter-related physiological systems that results in a depletion in homeostatic reserve and vulnerability to disproportionate changes in health status after relatively minor events such as changes in medication, or a minor operation or minor infection [4]. It is estimated that one in ten people over 65 years, and between a quarter and a half of those aged over 85 years are frail [4]. The conceptualisation of frailty as an abnormal health state, related to the ageing process, has emerged over the last 15 years, and robust models been developed and validated to identify and severity grade frailty. The two principle models of frailty are the phenotype [5] and the cumulative deficit [6] models. The phenotype model includes five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. Frailty is identified if three or more of these variables are present. The cumulative deficit model was originally derived from the Canadian Study of Health and Ageing (CSHA) and is based on the accumulation of 'deficits', with increasing numbers of deficits leading to increasing frailty. Examples of deficits include, symptoms (eg, low mood), signs (eg, tremor), and abnormal laboratory values, disease states, and disabilities [4]. There is increasing recognition that frailty should be viewed as a long-term condition [7].

Evidence from cross sectional data suggests that older adults with the most severe pain are significantly more frail than those with no pain or less severe pain [8]. It has been proposed that persistent pain may contribute to, or accelerate the development of frailty in older people through mechanisms such as impaired mobility, depression, decreased nutritional intake and

the burden of co-morbidities [9, 10], and interventions to improve pain management may help prevent frailty [11].

Pain is a subjective sensation with a complex, non-linear relationship between nociceptive information and pain perception [12]. Numerous methods of pain assessment have been developed. These are mostly self-report measures that typically include the identification of the pain site(s); pain intensity; descriptors to capture the sensory and affective components of pain; and an assessment of the impact on quality of life or intrusiveness such as interference with work inside and outside of the home. Pain is a significant, often unmet need in older people which can impact on their quality of life and mood [13, 14]. Understanding pain in older people with frailty is an important first step towards developing appropriate interventions specifically for this population.

Aims of this review

Firstly, to identify studies which assessed pain in older people reliably characterised as frail, and any reported associations between frailty and pain. Secondly, to identify biologically plausible mechanisms which may alter pain perception or contribute to, or exacerbate, pain in a frail older person. Thirdly, to identify specific implications of pain management for older people with frailty.

Methods

We identified cohort and cross sectional studies reporting on pain in community-dwelling older people (mean age > 65 years) that had included a validated frailty measure such as the phenotype [5], or the cumulative deficit model [6]. We excluded studies which only reported a frailty indicator measure, for example gait speed or the timed up-and-go test. Whilst these indicators demonstrate high sensitivity for the identification of frailty, they have poor specificity [15] and are therefore unsuitable for epidemiological research. Mood (anxiety and depression) was also included as an outcome of interest as frailty and its associated

functional impairment are risk factors for depression [16] Analgesic outcomes were also identified.

We developed a structured search strategy using controlled vocabulary and text words to search databases including CINAHL, Medline, Embase and Web of Science. We combined search terms for 'Pain' and 'Frailty' and 'Elderly'. Search strategies are available on request from the authors. This search strategy also identified a parallel literature describing pain more generally in older people that included possible mechanisms for pain in older people with frailty, and issues related to pain management in this particular population of older people. These aspects were reviewed separately.

Results

The review process is summarised in figure 1. We identified seven studies which reported pain outcomes in older people with frailty (table 1). One study was conducted in Canada[11, 17], one in Australia [18, 19], one in Finland [20], two in Taiwan [13, 21], and two in Brazil [22, 23]. The mean age of participants ranged from 71 years to 82 years (see table 1). Six studies had mixed sex populations. The Concord Health and Ageing in Men Project (CHAMP) study only recruited males [18, 19]. The CHAMP study [18, 19] measured frailty using the cumulative deficit model. The remaining studies used the phenotype model. All studies reported participants as not frail (fit or robust), pre-frail (an intermediate state), and frail. The proportion of frail participants ranged in the studies from 9% to 32%. Four studies used questions from the SF-12 or SF-36 to assess pain [11, 13, 19, 23]. Chang et al. [21] reported the presence of pain history but did not report the specific measure. The Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study investigated the presence and severity of musculoskeletal pain, and chronicity [20]. The frailty in the Brazilian elderly (FIBRA) study [22] used the Western Ontario and McMaster Universities Questionnaire (WOMAC). All the studies reported pain data at one time point. In the FIBRA study [22], participants all had, or were suspected of

having, osteoarthritis of the knee or hip. The remaining studies recruited older people without specific conditions. Three studies reported pain intensity [13, 20, 23].

Pain outcomes

In the Canadian Study of Health & Aging-Wave 2 [11, 17], approximately 16% of non- frail, 34% of pre-frail, and 50% of frail participants reported moderate pain or greater. Overall frailty status was significantly associated with pain self-report. For those with moderate or greater pain compared to those with no pain, or very mild pain, the odds of being pre-frail or frail compared to not frail were significantly higher.

In the CHAMP study (16) (n = 16704), approximately 17% of non-frail participants reported intrusive pain, 26% of men in the pre-frail category, and over 40% of those with frailty. Frailty status was significantly associated with reporting intrusive pain. Associations between pain, frailty and comorbidity found that those with the highest overall health burden (frail plus high comorbid burden) were most likely to report persistent pain. A strong association between frailty and intrusive pain remained after accounting for opioid use and depression.

In the Chang study [21], over 40% of frail older people reported pain, compared to approximately 20% of non-frail older people. In the FIBRA study [22], mean and median pain scores were non-significantly higher in the frail group. In the GeMS study [20], over 60% of frail participants had musculoskeletal pain compared to approximately 45% of non-frail participants. Furthermore, significantly more frail and pre-frail participants rated their pain as moderate/severe compared to non-frail. There was no significant difference in those who suffered with chronic pain (> 3 months duration) across the three groups. Lenardt [23] and Lin [13] used used the pain domain of the SF36 quality of life measure. Both studies found significantly lower quality of life in the pain domain. The Lin study [13], demonstrated that over 70% of frail participants reported pain compared to 48% of non-frail.

Analgesic consumption and frailty

Two studies reported analgesic consumption according to frailty status. In the CHAMP study [19] it was reported that opioid use varied by frailty status with 6.5% of frail men using opioids compared with 2.4% of pre-frail, and 1.2% of not frail men. In the GEMS study [20], there was a significant increase in analgesic use for increasingly levels of frailty, and use of opioids and acetaminophen (paracetamol)was significantly more prevalent in pre-frail and frail participants compared to non-frail participants. There was no significant difference in the prevalence of use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) between the different frailty states.

Depression

Four studies reported depression data for the different frailty states. In the Canadian Study of Health and Ageing, for older people with depressed mood, the adjusted odds (OR) of being frail to not frail were higher by a factor of 4.13 (95%CI 3.34, 5.12) [11]. In the FIBRA study [22], three (17.6%) non-frail older people self-reported depression compared with 15 (53.6%) pre-frail and seven (61.5%) frail older people. ($p = 0.041$). However, data derived from the geriatric depression scale (GDS), found no significant association between frailty and the presence of depression ($p = 0.118$). In the Chang [21] and Lin [13] studies, there were significantly more participants with depression in the frail and pre-frail categories compared to those in the non-frail group.

Anxiety

Lin [13] reported health related quality of life (SF - 36) in the domain of mental health and found that being frail or pre-frail was associated with significantly lower mental health related quality of life compared to be being non-frail ($p < 0.001$). The CHAMP study [18] reported anxiety data using the Goldberg Anxiety and Depression scale, and assessed worry about health. They reported strong association between worry about health and pain that was both persistent and intrusive, and that remained after accounting for age, number of

comorbidities, depression, self-rated health status, arthritis, and gait speed (adjusted odds ratio 2.9; 95% CI 1.8, 4.7), $p < 0.0001$). The corresponding adjusted odds ratio for the association between anxiety and pain was 2.3 (95% CI 1.0, 4.8; $p = 0.036$). Results were not reported for the different frailty states.

Pain mechanisms in people with frailty

There were several potential biological mechanisms described that might account for the increased prevalence of pain in older people with frailty compared to fit people. Firstly, frailty is associated with physiological changes which could theoretically alter pain perception or exacerbate pain in an older person. Changes occur in the brain, immune system, endocrine system and the skeletal system [4]. Secondly, age related changes in the neurophysiology of nociception and the perceptual experience of pain have been reported, including the reduced efficacy of the endogenous analgesic system in older people [24]. The diffuse noxious inhibitory control (DNIC) is a pain modulating process controlled by endogenous opioids which works via descending inhibition such that a noxious stimulus in one part of the body inhibits perception of a second painful stimulus [25-28]. Studies utilising experimental pain models on humans have reported age-related differences in this process whereby a first pain fails to modify a second pain, but instead enhances it [29-31]. Age-related increase in pain threshold (the least experience of pain a person is able to recognise) have been reported [24, 32]. This decreased sensitivity to pain has potentially important implications placing the older person at greater risk of injury [24].

Discussion

Although pain has been extensively studied in older people, we identified only seven studies which reported pain in populations of older people with well-defined frailty. This is perhaps unsurprising as robust, validated measures of frailty have only been developed in recent years. From the limited data available, it would appear that the presence of pain is higher in older people with frailty compared to people characterised as pre-frail or not frail. Thus older

people reporting pain are statistically more likely to be frail. Critically, however, a lack of prospective data precludes inferences about the direction of the relationship: that is whether pain or frailty is the antecedent. There was little information regarding the source of the pain other than the one study with a particular focus on musculoskeletal pain [20], and one which only recruited participants with osteoarthritis of the knee and hip [22]. Furthermore, there were only two studies which reported analgesic consumption according to frailty status and these did not include information on the perceived efficacy of the medication or possible adverse events. Therefore, there remains little information to determine what proportion of older people with frailty are in receipt of medication, and whether this medication is adequate.

Mood state can impact on persistent pain and older people with frailty experience more anxiety and depression than non-frail people [16, 33]. The extent to which this is related to more frequent external stresses such as the loss of friends, or family support, or a greater reaction to these losses due to the abnormal health state of frailty and impaired resilience is unclear. Anxiety may contribute to, or exacerbate pain in frail older people. Anxiety is associated with subjective feelings of apprehension about impending or anticipated harm [34], autonomic arousal (increased heart rate) and avoidance behaviour. Both state and trait anxiety can result in increased pain sensitivity, increased report of pain intensity and reduced pain tolerance [34-39]. Negative expectations of pain, or pain worsening, induce anticipatory anxiety about the impending pain, thus triggering the activation of the neuropeptide cholecystokinin which can facilitate pain transmission [40]. In the CHAMP study, there was a strong association between persistent and intrusive pain with worry about health and overall anxiety [18]. However, within this review there was a lack of anxiety data, reported by frailty status, to draw any conclusions with the role of anxiety and pain in this particular population.

Depression was reported for the different frailty states in four studies. From the limited data available for this review, the presence of depression appeared to higher in frail older people

compared to fit older people. The relationship between depression and pain is complex. Pain is both an antecedent and consequence of depression [41]. From a neurobiological perspective, pain processing and mood are controlled by common neurotransmitters including norepinephrine which contributes to pain inhibition via descending pathways of the central nervous system. Avoidance and withdrawal behaviours, common in both pain and depressed populations [41] could be relevant. The fear avoidance model of pain proposes that when a person perceives pain as threatening they typically respond with pain related fear avoidance behaviour [42] which results in decreased functioning and disability [43]. A recent meta-analysis identified a strong association between pain related fear and disability [42] but because only cross-sectional studies were included, inferences about the direction of the relationship were precluded. However, as frailty is often combined with disability and comorbidity [42], and the overlap increases with greater frailty [44], there is an obvious substrate for a perpetuating cycle of pain, depression and immobility, thus compromising the life of the older person.

Frailty is associated with an increased risk of delirium [45], cognitive impairment [46], and dementia [47]. The frail person who presents with one of these conditions is a particular challenge for appropriate pain assessment. A cognitively impaired person, or a person who cannot readily articulate their pain, may be unable to use traditional numeric or verbal pain rating scales [48]. This can result in under-recognition of pain and subsequent inadequate pain treatment management for older patients with cognitive impairments [49]. It has been proposed that older, frailer, and more cognitively impaired people receive the least treatment for pain, even though that population has the greatest need for assistance [50]. Within this review, analgesic consumption appeared to be higher in people with frailty compared to fit older people, although limited data precludes strong conclusions.

Older people with frailty tend to be high users of health services. Therefore, there should be reasonable existing opportunities to assess and manage pain. However, the higher presence

of pain in the frailer adults compared to fit older adults, identified in this review suggests that pain may be an unmet need for many of this group. This could be as a result of factors that include decisions by the older person or by their clinician. One of the challenges of treating pain appropriately in older people with frailty is they often have multiple comorbidities and are in receipt of multiple medications [51]. Personal decision making regarding the use of pain medication has been reported in qualitative studies of older people where pain medication may not be considered a priority by the older person already taking multiple medications for multiple conditions [52]. However, it was reported within the GeMS study, that nearly half of the older people with frailty wanted their doctor to pay greater attention to pain management.

There are factors that may potentially influence clinicians' decisions regarding prescribing analgesia. Concerns over the use of opioids in older people still persist [53]: a recent review failed to identify any comparative studies investigating the effectiveness of opioids for the treatment of chronic malignant and non-malignant pain in older populations [51]. Furthermore, changes in medication can often have a disproportionate impact on the frail older person, thus altering their health state negatively [4]. People with frailty tend to have less predictable drug responses, increased drug sensitivity, and the potential for harmful side effects [51]. A recent review of the clinical pharmacology of analgesic medicines in older people with frailty, suggest that frailty may be predictive of an individual's pharmaco-kinetic and pharmacodynamics response, however, there are limited data examining this [54].

Recommendations

The relationship between frailty and pain has not been well studied and warrants further attention. In particular, there is a need for prospective studies which follow a well-defined cohort of older people over a number of years and include robust measures of frailty and pain. These studies will provide useful information to determine if pain as an important potential stress factor contributes to the development of, or acceleration, of frailty or, alternatively, if frailty predisposes to pain.

Furthermore, there is a need to investigate pain interventions in a well-defined frail population. Currently, there is an under representation of older people in clinical trials despite this population having a disproportionally higher disease burden and higher medication consumption compared to the rest of the population. Under-recruitment of older people into randomised controlled trials is partly due to exclusion criteria, ethical dilemmas, and patient preference [55]. Trial designs such as the cohort multiple Randomised Controlled Trial (cmRCT) may provide a solution to the recruitment of older people [55]. This design incorporates a cohort of people with the condition of interest (in this case frailty), and scheduled follow up, as well as providing a platform for intervention studies. The inclusion of older people based on their frailty status, rather than their chronological age, will provide useful information to clinicians so they can be better informed on the benefits and risks of interventions in this population.

Basic science studies utilising established pain models could provide information on the changes that occur in nociception in later life, and the extent to which descending pain modulating become compromised in older adults with frailty. To date, basic science research studies have failed to include the “oldest old” and typically involve adults between the ages of 65 and 75 years [56]. Whilst age is not necessarily an indicator of frailty, rates of frailty increase with age, and the inability of studies to include the “oldest old” precludes inferences specifically for a frail population [57].

The pain measures that were included in the studies identified for this review were largely based around single questions and, whilst providing useful short measures of pain, they provide limited information on the underlying causes of pain, or the experience of the older person with frailty in pain and how pain impacts and compromise their lives. Qualitative studies could help to answer some of these questions. Leading on from this, understanding more about the communication that occurs between GPs and older people with frailty during

consultations around pain and analgesia may provide useful information on the challenges of managing pain within this particular population.

Acknowledgements

Thanks to Deirdre Andre from the University of Leeds for undertaking the search for this review.

This article presents independent research by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Yorkshire and Humber (NIHR CLAHRC YH), www.clahrc-yh.nihr.ac.uk. The views and opinions expressed are those of the authors, and not necessarily those of the NHS, the NIHR or the Department of Health.

Financial support

LB, AC, JY and AH receive funding through the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Yorkshire and Humber (NIHR CLAHRC YH), www.clahrc-yh.nihr.ac.uk.

Conflict of interest

None

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Title 1: Pain outcomes for not fit (not frail), pre-frail and frail older people

Title	Country	n	Age mean (SD)	% female	Frailty measure	Pain measure	Fit (not frail, robust) Pre-frail Frail n (%)	Pain data by frailty status	Reported associations between frailty and pain	Depression or anxiety reported by frailty status	Analgesic consumption reported by frailty status
Canadian Study of Health and Aging-Wave 2 (11, 17)	Canada	4968	79.7 years (6.1)	61.5%	CDM	**Bodily pain (SF - 36)** "*How much bodily pain have you had during the past 4 weeks?*" The response categories were presented on a card vertically in ascending order: 1 = none, 2 = very mild, 3 = moderate, 4 = severe and 5 = very severe. Pain status dichotomized: no pain & very mild pain versus moderate, severe, or very severe pain	Fit: 1663 (33) Pre-frail: 1728 (35) Frail: 1577 (32)	Fit: None or mild pain 1378 (43%), ≥ moderate pain 285 (16.2%) Pre-frail: None or mild pain 1127 (35.2%), ≥ moderate pain 601 (34.1%). Frail: None or mild pain 698 (21.8%) ≥ moderate pain 879 (49.8%)	For persons with moderate or greater pain compared to those with no pain or very mild pain, the odds of being pre-frail compared to fit were higher by a factor of 2.52 (CI = 2.13-2.99; $p < 0.05$) For persons with moderate or greater pain compared to those with no pain or very mild pain, the odds of being frail compared to not frail was higher by a factor of 5.52 (CI = 4.49-6.64; $p < 0.05$)	Yes	No
The Champ Study (18, 19)	Australia	1674	76.9 (SD 5.48)	0%	Phenotype	**Intrusive pain (SF - 12)** "*During the past four weeks, how much did pain interfere with your normal work (including both work outside the home and housework*?" Responses grouped: Not at all/a little bit versus.	Fit: 837 (50) Pre-frail: 679 (40.6) Frail: 158 (9.4)	Fit: 141 (16.8%) Pre-frail: 179 (26.3%) Frail: 69 (43.9%)	Frailty status was significantly and incrementally associated with reporting intrusive pain with unadjusted odds ratios for pain of 1.8 ($p < 0.0001$) in pre-frail men and 3.9 ($p < 0.0001$) in frail men, compared to fit men. Men with the highest overall health burden (frail plus high	No	Yes

						Moderately/quite a bit/extremely			comorbid burden) were most likely to report intrusive pain (adjusted odds ratio 3.0 (95% CI 1.6–5.5), p = 0.0004)		
Chang (21)	Taiwan	275	71.1 (3.8)	53.8%	Phenotype	**Pain history** (affecting daily life and sleep - measure not reported)	Fit: 81 (29.5) Pre-frail: 161 (58.5) Frail: 31 (11.3)	Fit: 16 (19.8%) Pre-frail: 52 (32.7%) Frail: 13 (41.9%) Unknown: 2		Yes	No
FIBRA (22)	Brazil	58	74.0 (5.5)	93%	Phenotype	**WOMAC (Western Ontario and McMaster Universities)** Pain in last 72 hours (0 - 20 scale) Mean (SD) Median	Fit: 17 (29.3%) Pre-frail: 28 (48.2) Frail: 13 (22.4)	Fit: 34.1 (20.3) 35 Pre-frail: 35.7 (21.9) 35 Frail: 43.9 (28.8) 45	ANOVA F = 0.716, p = 0.493	Yes	No

GeMS (20)	Finland	605	81.9 (4.5)	70%	Phenotype	The presence, severity and duration of **musculoskeletal pain** (previous month). **Pain Intensity** 1–10 numeric rating scale, (1 indicated no pain and number 10 indicated excruciating pain.). Grouped as 2–4 = mild pain, 5–10 = moderate to severe pain. **Chronic pain** defined as > 3 months duration.	Fit: 237 (39.1) Pre-frail: 299 (49.4) Frail: 69 (11.4)	58.5 % of pre-frail and frail participants reported pain during the previous month. Musculoskeletal pain: Fit 106 (44.7%) Pre-frail 173 (58.1%) Frail 41 (60.3%) Pain intensity No pain: Fit 131 (55.3), Pre-frail 125 (41.9), Frail 27 (40.3) Mild pain: fit 59 (24.9), Pre-frail 71 (23.8), Frail 16 (23.9) Moderate/severe pain: fit 47 (19.8), Pre-frail 102 (34.2), frail 24(35.8) Chronic pain Fit: 89 (37.6) Pre-frail: 155 (52.0) Frail 35 (50.0)	44.3 % (n = 47) of not-frail participants with pain, rated their pain as moderate/severe whereas a higher proportion of pre-frail (59.0 %, n = 102) and frail (60.0 %, n = 24) rated their pain similarly (p = 0.043) Frail participants were significantly more likely to use analgesics than fit participants even after adjusting for age, sex, MMSE score and skeletal pain (OR 2.96; 95 % CI 1.38, 6.36) No significant difference between frailty groups for the numbers with chronic pain.	No	Yes

****Lenardt (23)**	Brazil	203	70.9 (7.4)	51.3%	Phenotype	Brazil **SF - 36** Bodily pain Mean (SD) Higher score = higher quality of life	Fit 49 (24.1%) Pre-frail 115 (56.7%) Frail 39 (19.2%)	Fit: 78.9 (24.6). Pre-frail: 62.5 (31.8). Frail: 60.4 (30.7) p = 0.002 (Kruskal-Wallis)		No	No
Lin (13)	Taiwan	933	73.9 (6.3)	48%	Phenotype	**Pain problem**. Question with binary response (details not reported) **Bodily pain SF - 36** (2 items) Higher score = higher quality of life	Fit: 426 (45.66) Pre-frail 415 (44.48) Frail 92 (9.86)	Pain problem Fit: 196 (47.7%) Pre-frail 226 (56.6%) Frail: 63 70.9% p <0.001 SF - 36 Bodily pain - adjusted mean (SE) Higher score = lower pain Fit: 83.49 (1.34) Pre-frail 81.23 (1.26) Frail 74.29 (1.99) F = 8.89, p < 0.001 Adjusted for age, gender, education, marital status, chronic disease, pain		Yes	No

								problem, sleep impairment, regular exercise, smoking and drinking behaviours.			

CDM= cumulative deficit model

n = number included in analysis

** additional data obtained from correspondence with the author