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Pain and its clinical associations in individuals with cystic fibrosis: A systematic review

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Abstract

Pain is recognized as a clinical complication in cystic fibrosis (CF), but the prevalence, characteristics and clinical associations of this co-morbidity have not been systematically reviewed. Electronic searches of six databases were performed. For inclusion in phase 1, studies reported a pain prevalence rate in CF and/or its clinical associations. For phase 2, included studies reported the measurement properties of validity, reliability and responsiveness of an instrument assessing pain in CF. Two independent reviewers rated the quality of evidence (phase 1) and the measurement properties using the 4-point COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist (phase 2). Of the 400 studies identified in the literature, 16 met the inclusion criteria for phase 1 and 5 for phase 2. The mean (SD) quality score (of 16) was 11.8 (2.3). The pooled prevalence of pain in adults with CF was 77% (95% confidence interval (CI): 57%–92%) and in children was 42% (95% CI: 0%–91%). Common regions of pain included back, abdomen, chest and limbs. In children and adults, pain was associated with a poorer quality of life (QOL) and significant interference with treatments. Measurement properties of three instruments (Brief Pain Inventory, Multidimensional Pain Inventory, Daily Pain Assessment-CF) were construct validity and criterion-predictive validity, with variable findings based on 'fair' to 'good' quality studies. Pain is a common problem in both children and adults with CF. It has negative clinical associations with QOL and the ability to successfully undertake treatment. Further research exploring the measurement properties of instruments assessing pain is required.

Keywords

Cystic fibrosis, prevalence of pain, clinical symptoms, measurement, quality of life

Introduction

Cystic fibrosis (CF) is frequently characterized by chronic cough, purulent sputum production and fatigue, all of which contribute to impaired health-related quality of life (HRQOL) and reduced exercise tolerance.[1] In adults and children with CF, pain has emerged as an important feature of the overall clinical profile, reported to affect up to 75% of children[2–4] and 89% of adults,[5,6] a higher prevalence compared to reports of chronic pain in the general population, which ranges from 11% to 64%.[7,8] Pain is commonly located in the spinal and chest wall regions.[2,3,5,9] Whilst a recent narrative review of pain in this population highlights the emerging interest in exploring the broad features of this co-morbidity,[10] a systematic review of pain prevalence in children and adults with CF, which includes methodological assessment of studies and determines the clinical manifestations has not been undertaken.

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The measurement of pain is complex. It is therefore important to determine whether the available assessment tools capture all its dimensions. Whilst the tools frequently used to identify pain in CF have been previously outlined,[6,10] an analysis of their measurement properties has not been undertaken. This knowledge will assist clinicians in selecting the instrument best suited to assess pain in CF.

Therefore, the primary aim of this systematic review was to establish the prevalence of pain and its characteristics in individuals with CF and to determine the association between pain and clinical features of CF. The secondary aim was to explore the measurement properties of instruments assessing pain.

Methods

This review is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[11] and was registered with PROSPERO (42015017681). Phase 1 aimed to identify the prevalence of pain in CF and its association with clinical features. Phase 2 identified instruments used to assess pain in CF and their measurement properties.

Phase 1 – Prevalence and clinical associations

Search strategy. A systematic literature review was undertaken by one author of the following databases: MEDLINE, CINAHL, AMED, EMBASE, Pubmed and Cochrane Library of Systematic Reviews from inception to February 2015. The keywords included 'pain', 'musculoskeletal pain', 'neck pain', 'chronic back pain', 'shoulder pain', 'abdominal pain' and 'prevalence', or 'symptom' and 'prevalence' in combination with each of the following terms: 'cystic fibrosis or 'CF' or cystic fibr*' in the title, abstract or keywords and was adapted for each database. An example of an electronic search as applied in MEDLINE is outlined in online Supplemental data 1. Reference lists of the retrieved articles were inspected manually to identify any additional papers. Authors were contacted for information where necessary.

Inclusion criteria. Titles and abstracts of citations were assessed for inclusion eligibility by two independent reviewers (ALL and SR). Full-text articles were retrieved and reviewed against the inclusion criteria. Disagreement regarding eligibility for inclusion, at both the title/abstract and full-text review stage, was resolved by consensus. Figure 1 illustrates this process.

Studies were included if they reported on the prevalence of pain and/or its clinical impact in either an adult or paediatric population diagnosed with CF (in a stable clinical state or acute exacerbation) and were written in English. Observational cohort, case–control, cross-sectional studies of a retrospective or prospective design were included. Exclusion criteria were case studies, dissertations or publications only in abstract form due to the limited ability to accurately assess methodological quality. As translation services were not available, studies in a language other than English were also excluded.

Reports of pain prevalence included point prevalence and pain in the past week/months/years. Data related to pain severity, frequency and/or duration, description and location were collated. Outcomes were self-reported or clinically evaluated. Information related to impact or interference of pain on activity, exercise capacity, symptoms (physical and psychological), treatment and HRQOL were primary outcomes. Secondary outcomes were the relationship of pain to lung function and co-morbidities and treatment strategies implemented.

Quality assessment. For case–control, cross-sectional and cohort studies, the Critical Review Form – Quantitative Studies was applied by two independent reviewers (ALL and KB). This appraisal tool evaluates method rigour and bias using a combination of dichotomous (yes/no) and descriptive items.[12] The decision to select a yes/no score was based on the raters' experience, instructions accompanying the tool and applicability of the domains relative to the design of the study appraised. Any disagreements between the reviewers were resolved by consensus. An arbitrary quality score was obtained by totalling 16 relevant dichotomous quality appraisal criteria in this tool, with a score of 1 indicating fulfilment of the criterion and a score of 0 indicating non-fulfilment or non-description of the criterion.

Data extraction. Extraction of data was performed by one investigator (ALL) using a standardized template, which was checked by a second investigator (SR). Extraction included participant details, pain prevalence, pain intensity/severity, frequency and duration and pain location. For clinical associations of pain, the degree of interference or interaction with exercise

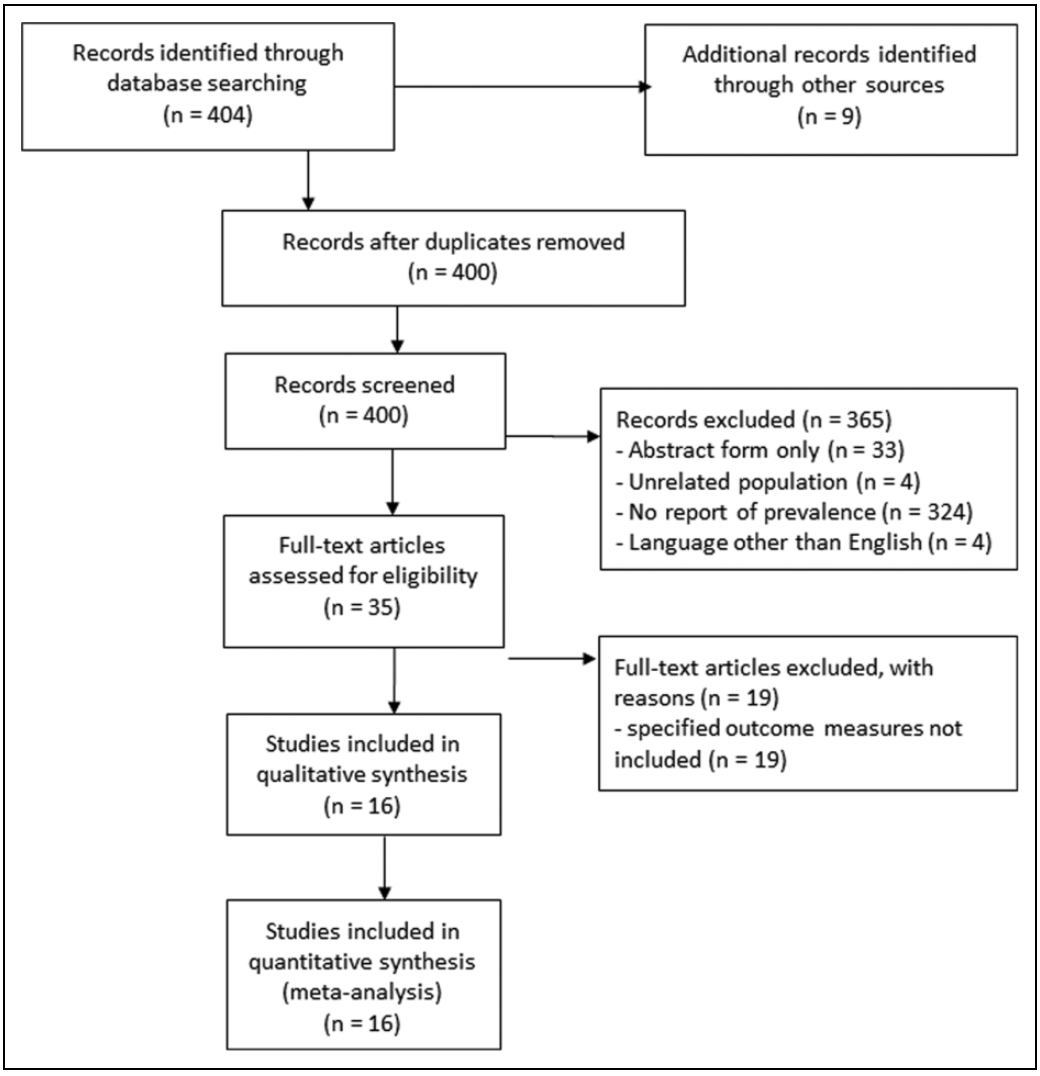

Figure 1. PRISMA flow diagram of study selection process.

capacity, physical activity or function, symptoms of dyspnoea or fatigue, HRQOL and psychological symptoms (anxiety, depression and fear related to movement) were extracted. The relationship between pain and lung function or other measures of disease severity was also identified. Authors were contacted when necessary to obtain further information.

Phase 2 – Instrument measurement properties

Search strategy. A similar strategy of the same databases applied in phase 1 was undertaken by one author (ALL), with an example of the strategy applied in MEDLINE detailed in online Supplemental data 2. Both unidimensional and multidimensional instruments measuring pain were included. Search terms were customized for each database, with a validated sensitive search filter for finding studies on measurement properties of instruments applied.[13]

Inclusion criteria. Following removal of duplicates, studies were screened by two reviewers (ALL and KB). This included screening of titles and abstracts from all retrieved studies followed by full-text review of potentially eligible studies, based on the inclusion criteria. Inclusion criteria consisted of participants with diagnosis of CF, instrument designed to measure the presence of pain and information reported for one or more measurement properties: reliability, internal consistency, measurement error, criterion concurrent validity, criterion/predictive validity, construct validity/hypothesis testing and responsiveness.[13]

Data extraction and quality assessment. Data were extracted using a standardized template. Two

independent reviewers (ALL and KB) evaluated the study quality using the COSMIN checklist.[14] This is a validated tool comprised of 10 sections, each scoring the quality of one measurement property. Within each section, items are individually scored based on a 4-point scale (excellent, good, fair or poor), with an overall quality score for each property obtained using the lowest score recorded among the items, as recommended.[14]

Analysis

Analysis of pooled pain prevalence was based on the response to a question of 'do you have pain?' in any instrument used, whilst analysis of pain locations was based on the proportion of participants who reported experiencing pain in selected areas. For studies that reported outcomes for the same series of patients,[3–5] the reported prevalence was included only once in the meta-analysis. The pooled prevalence of pain and pain locations (where common regions were identified) were analysed using MetaXL 1.3, a tool for meta-analysis in Microsoft Excel (http://www.epigear.com/). The data were first transformed using the variance stabilizing double arc sine transformation.[15] The quality effects model was then applied to determine the odds ratio (OR) and 95% confidence interval (CI). This model was selected over the fixed- or random-effects models to explicitly address heterogeneity in pooled proportions caused by differences in study quality as well as differences in distribution.[16,17] It is a modified version of the fixed-effects inverse variance method, which additionally allows giving greater weight to studies of high quality. MetaXL ensures that the pooled proportions add up to 1. Heterogeneity assumption was assessed by χ^2-based Q-test and I^2 test. Results related to clinical implications of pain were reported narratively.

Results

Phase 1 – Prevalence and clinical associations

A total of 404 papers were identified; references checked of included papers found an additional 9 papers. Following the removal of 13 duplicates, a total of 400 titles and abstracts were reviewed. Of those, 35 full texts were reviewed, with a total of 16 papers included (Figure 1).

Quality assessment. For the 16 papers, the mean (SD) quality score of quantitative studies[10] was 11.8 (2.3) (Table 1). Common methodological flaws were sampling biases, absence of sample size calculation and the use of instruments for which validity and reliability were not established.

Study characteristics. Study characteristics are outlined in Table 2, with one author contacted for further information.[27] A total of 1665 patients in a stable state were included, with disease severity ranging from a forced expiratory volume in one second of 27%–81% predicted. One study included a comparative group of healthy controls,[18] whilst two studies included both children and adults with CF.[6,25] One study explored pain experiences in adults during an acute exacerbation as well as a stable clinical state.[5] Two studies attributed pain experiences to treatment, including airway clearance therapy, medical procedures and lung function testing.[2,3]

There was considerable variability in the definition of musculoskeletal pain in the included studies upon which prevalence was based. Seven studies used self-reported questionnaires to identify the presence of pain (yes/no).[3,4,6,18,25–27]In five studies, pain prevalence was determined by validated instruments in the form of the Brief Pain Inventory (BPI),[5,9,24] the Multidimensional Pain Inventory (MPI)[20] or the Pain Disability Index.[22] A single study applied the criteria of a significant pain event in the medical record requiring medical intervention[19] whilst one determined prevalence from a symptom questionnaire.[23]

Most studies used clearly stated recall periods for pain. Prevalence was established based on experiences of pain within the last week,[2,3,5,9,27] the last month,[4,6,21,25] previous 2 months,[26] previous 3 months[18] or previous 9 years.[22] Overall, the pooled prevalence in adults was 77% (95% CI: 57%–92%; Figure 2) and in children was 42% (95% CI: 0%–91%; Figure 3). The heterogeneity of I^2 of 97% and 98% suggests strong variability between studies. Compared to healthy controls, prevalence was greater in CF (43% vs. 14%).[18]

Common descriptors of pain included sore, aching, cramping and stiffness in one study of children.[2] Ravilly and colleagues[19] reported aetiology of chest pain (e.g. pleuritic, muscular, fractured ribs or pneumothorax), back pain (muscular, ligamentous or referred) and limb pain (arthritis or other orthopaedic conditions), whilst Rose and colleagues attributed pain to evidence of vertebral wedging.[18]The pooled prevalence of back pain was 39% (95% CI: 24%–56%),[5,6,9,18,19,24–27] abdominal pain was 34% (95% CI: 17%–52%),[2,3,6,9,18,19,24–26] chest pain was

Table 1. Quality assessment of observational studies.

Study	Quality appraisal score[a]																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total
Rose et al.[18]	✓	✓	✓	✓	×	✓	×	×	×	×	×	✓	✓	✓	✓	✓	10
Ravilly et al.[19]	✓	✓	✓	✓	×	✓	×	×	×	×	✓	✓	✓	✓	✓	×	10
Epker et al.[20]	✓	✓	✓	×	×	×	×	✓	×	×	×	✓	✓	✓	✓	×	8
Festini et al.[21]	✓	✓	✓	✓	×	✓	×	✓	×	×	✓	✓	✓	✓	✓	✓	12
Hubbard et al.[22]	✓	✓	✓	×	×	×	✓	×	×	×	×	✓	×	✓	✓	×	7
Koh et al.[3]	✓	✓	✓	×	×	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	12
Palermo et al.[4]	✓	✓	✓	×	×	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	12
Sawicki et al.[23]	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	14
Flume et al.[24]	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	12
Sermet-Gaudelus et al.[25]	✓	✓	✓	×	×	✓	×	×	×	✓	×	✓	✓	✓	✓	✓	10
Stenekes et al.[6]	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14
Hayes et al.[9]	✓	✓	✓	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	13
Munck et al.[26]	✓	✓	✓	×	×	✓	×	✓	✓	×	✓	✓	×	✓	✓	✓	11
Kelemen et al.[5]	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	15
Blackwell and Quittner[2]	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	15
Michel-Cherqui et al.[27]	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	13

[a]Key to scoring (Law et al.[12] all items ✓ for yes, × for no, except biases (× for yes, ✓ for no). 1 = Was the study purpose stated clearly?; 2 = Was relevant background literature reviewed?; 3 = Was the design appropriate for the study question?; 4 = Were there any biases present (minimum response rate of 80% for sample bias, blinding of investigators when physical measure were taken)?; 5 = Was sample size justified?; 6 = Was the sample described in detail? (had to include the number of participants by gender, age, and a description of where the cohort was sampled from); 7 = Was informed consent obtained? (if not described, assume no); 8 = Were the outcome measures valid? (if all not described, assume no); 9 = Were the outcome measures reliable? (if all not described, assume no); 10 = Results were reported in terms of statistical significance?; 11 = Dropouts were reported?; 12 = Clinical importance was reported?; 13 = Were the statistical analysis methods appropriate?; 14 = Conclusions were appropriate given the study methods?; 15 = Are there implications for clinical practice given the results of the study (based on the experience of the reviewers)?; 16 = Were limitations of the study acknowledged and described by the authors?

29% (95% CI: 19–34%),[2,3,5,6,9,18,19,24–27] limb (upper and lower) pain was 24% (95% CI: 11–40%)[5,6,9,19,22,24,25,27] and cervical/neck was 23% (95% CI: 12%–37%).[2,3,5,21,24]

Specific pain characteristics for each study are outlined in Table 3. In children, four studies reported pain at its worst, ranging from 1.0 to 4.9 on visual analogue scale (VAS).[2–4,25] In children, the frequency of pain episodes varied from daily pain to less than once a month, with episodes as short as 30 minutes and as long as several days.[2,18,25,26] The overall duration of pain experienced in children was as long as 1 year.[18] In adults, the greatest pain intensity ranged from 1.1 to 6.9, according to numerical rating scale and VAS reported in seven studies.[5,6,20,22,24,25,] With episodes as frequent as up to 10 over 1 to 2 months,[20,27] the episode duration ranged from less than 2 h to up to 1 week.[22,25] Adults with CF had suffered from pain for as long as 5 years.[6,9]

Clinical associations. Clinical associations of musculoskeletal pain are described in Table 3. In children, pain characteristics (prevalence, intensity, frequency and duration) were not associated with disease severity,[3,25] those experiencing pain reported significant interference with respiratory symptoms (coughing and breathing)[2,4,18] and a greater degree of difficulty in performing physiotherapy, including airway clearance therapy, exercise and physical activity.[2,18,25] Pain was associated with a poorer HRQOL,[2,4] sleep disturbance,[25] absence from school[25] and higher levels of anxiety and depression.[2,26]

In adults, those who experienced pain reported greater interference with their respiratory symptoms,[5,9] and the ability to undertake effective physiotherapy.[24] Those with higher pain average scores were at greater risk of exacerbation (OR = 1.65, 95% CI: 1.03–2.64).[9] Those in a stable clinical state reported greater interference with exercise, whilst those experiencing an acute exacerbation found difficulty in completion of airway clearance therapy.[5] Pain was associated with reduced physical function, fewer social activities and recreational time and difficulty fulfilling family and work responsibilities.[5,9,20,24–26]

Table 2. Details of study characteristics.[a]

Study	Study design	Number of participants	Age (mean (SD)), gender	Disease severity (FEV_1% predicted), clinical state	Measurement tools
Rose et al.[18]	Case–control, prospective	CF: 50; control: 50	CF: 23 (10–36) years,[b] 44% female; control: 23 (10–26) years,[b] 44% female	CF: NR Control: NR	Questionnaires of recurring upper/mid/low back pain, reporting onset, location and duration. Pain intensity, changes with time, aggravating and easing factors.
Ravilly et al.[19]	Cross-sectional retrospective	Posthumous: 55; consulting: 23	Posthumous: 24 (7) years, 45% female; consulting: 23(5) years, 48% female	Posthumous: 27 (11) % pd, clinical state: NR; consulting: 58 (20) % pd, stable	Medical chart review of pain episodes. Location diagnosis of chest pain and rib fracture pain.
Epker et al.[20]	Cross-sectional, prospective	75	26 (9) years, 49% female	NR, stable	MPI Shwachman rating of illness severity
Festini et al.[21]	Cross-sectional	239	26 (18–23) years, [b]52% female	56.7 (23.3)% pd, stable	Standard questionnaire (location, frequency, intensity, treatment and effect on daily life).
Hubbard et al.[22]	Cross-sectional,	18	Age: NR; 67% female	NR	PDI PRI
Koh et al.[3]	Cross-sectional	46	13 (9) years; 52% female	80.2 (18) % pd, stable	Self-report questionnaire (duration, impact and frequency). FPS body chart for location
Palermo et al.[4]	Cross-sectional	46	13 (9) years; 52% female	80.2 (18); % pd, stable	CRQ-R Self-report Questionnaire (duration). FPS body chart for location
Sawicki et al.[23]	Cross-sectional	303	33 (13) years, 58% female	69 (28%); % pd, stable	MSAS
Flume et al.[24]	Cross-sectional	50	31 (18) years; 46% female	Pain: 59.1 (23.5) % pd, stable; No pain: 58.4 (22.5) % pd, stable	BPI PSQI
Sermet-Gaudelus et al.[25]	Cross-sectional	Children: 73; adults: 110	Children: 10 (5) years, 50% female; adults: 29 (7) years, 56% female	Children: 70 (21) % pd, stable; adults: 50 (26) % pd, stable	Self-report Structured Pain Questionnaire (duration, impact on absenteeism from school/work, asthenia, insomnia, physical activity or family life). Treatment (frequency and efficacy).

(continued)

Table 2. (continued)

Study	Study design	Number of participants	Age (mean (SD)), gender	Disease severity (FEV_1% predicted), clinical state	Measurement tools
Stenekes et al.[6]	Cross-sectional	Children: 64; adults: 59	Children: 7–17 years; % female NR; adults: >18 years; % female NR	Children/adults: NR, stable	Study questionnaire (frequency, severity of symptoms)
Hayes et al.[9]	Cross-sectional	83	29 (19–71) years,[b] 57% female	63.6 (27.6–134.0)[b] % pd, stable	BPI, PCS, CFQOL-R and HADS
Munck et al.[26]	Cross-sectional	130	14 (9–17) years, 75% female	85 (21)% pd, stable	Eland Pain location, FPS-R, McGill Emotional Scale, R-CMAS anxiety scale and CF-QOL
Kelemen et al.[5]	Cross-sectional	Stable: 73; acute exacerbation: 33	Stable: 29 (9) years; 45% female; acute exacerbation: 30 (11) years; 67% female	Stable: 60.5 (24.9) % pd; acute exacerbation: 47.3(14.9) % pd	BPI, PCS, CF-QOL
Blackwell and Quittner[2]	Cross-sectional	95	16 (3) years, 62% female	80.1 (25.9) % pd, stable	DPAQ-CF, body chart for location, HADS, MPR, CFQ-R
Michel-Cherqui et al.[27]	Cross-sectional	51	NR	NR, stable	Self-report questionnaire (current, maximal and average pain). Location.

FEV_1: forced expiratory volume in 1 second; NRS: Numerical Rating Scale; NR: not reported; FPS: Faces Pain Scale; CRQ-R: Cystic Fibrosis Questionnaire–Revised; DPAQ-CF: Daily Pain Assessment Questionnaire–Cystic Fibrosis; HADS: Hospital Anxiety and Depression Scale; MPR: Medication Possession Ratio; PDI: Pain Disability Index; PRI: Pain Response Inventory; BPI: Brief Pain Inventory; PSQI: Pittsburgh Sleep Quality Index; PCS: Pain Catastrophizing Scale; FPS-R: Faces Pain Scale–Revised; R-CMAS: Revised Children's Manifest Anxiety Scale; CRQOL-R: Cystic Fibrosis Quality of Life Questionnaire–Revised; MPI: Multidimensional Pain Inventory; MSAS: Memorial Symptom Assessment Scale.
[a]Data are *N* or mean (SD), unless otherwise stated.
[b]Median (range).

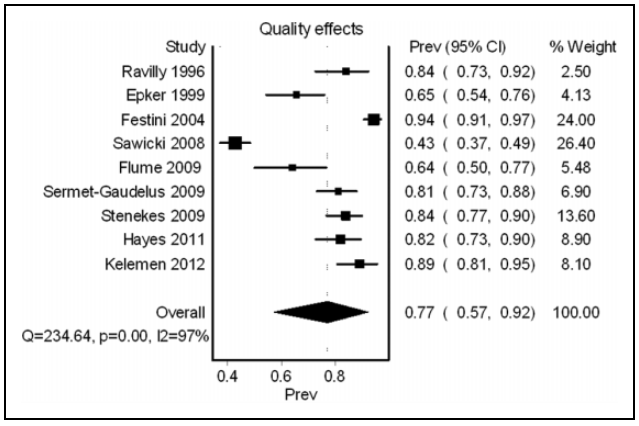

Figure 2. Pooled point prevalence of pain in adults with CF. CF: cystic fibrosis.

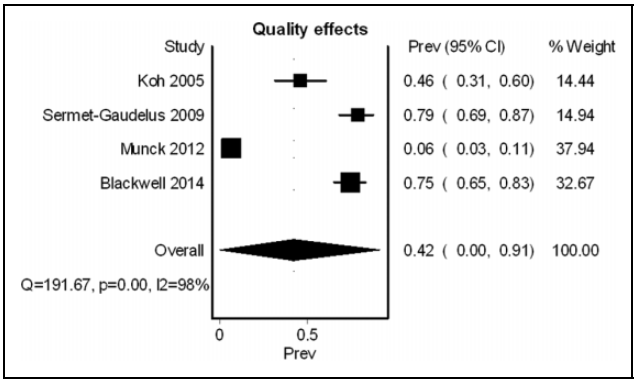

Figure 3. Pooled point prevalence of pain in children with CF. CF: cystic fibrosis.

Table 3. Pain characteristics and clinical associations.

Study	Prevalence	Pain regions	Pain intensity	Pain frequency and/or duration	Clinical associations
Rose et al.[18]	43% ($n = 22$)	Mid-back: 58%; lower back: 60%; both: 8%	Mild: 26%; moderate: 54%; severe: 20%	Frequency: daily: 26%, weekly: 30%, monthly: 24%, yearly: 16%; duration: <1 h: 6%, 1 day: 24%, 2–6 days: 26%, weekly: 4%	Pain interfered with breathing in 34%, coughing in 46%, exercise in 38%, work in 30% and ACT in 20% of people. Pain was associated with positioning in 50%, coughing in 44% and respiratory illness in 26% of people.
Ravilly et al.[19]	84% ($n = 46$)	Chest: 64%; headaches: 53%; limbs: 11%; abdomen: 11%; back: 16%;	NR	NR	NR
Epker et al.[20]	65% ($n = 49$)	Locations: NR	Mean 1.6 (1.3), reported by 65%	NR	A total of 63% reported a mild level of pain-related interference, while 17% reported no interference. Females with pain experienced higher severity ($p = 0.002$), more interference ($p = 0.005$) and greater affective distress ($p = 0.002$). Older age was associated with more pain interference (related to increased interruptions with family function, social and work-related activities; $r = 0.32$). Increased pain severity was associated with more severe respiratory history ($r = -0.24$).
Festini et al.[21]	94% ($n = 225$)	Back: 48%; chest: 32%; cervical: 28%; bones/muscle: 44%; headache: 63%; abdomen: 33%	Mild 1–3 (20%), moderate 4–7 (41%) and severe 8–10 (33%)[a]	Frequency (over 2 months): 1 episode: 13%, 2–5 episodes: 31%, 6–10 episodes: 20%, >10 episodes: 33%	38% of participants reported painful episodes in $\geq$4 locations. Pain restricted ability to carry out usual activities in 40%, with 16% unable to undertake usual activities. Pain linked to lost days of work or study in 22%, sleep disorders in 30% and failure to complete prescribed treatment in 11%.

(continued)

Table 3. (continued)

Study	Prevalence	Pain regions	Pain intensity	Pain frequency and/or duration	Clinical associations
Hubbard et al.[22]	55.6% ($n = 10$)	Chest: 72% and LL/joints: 61%	4.2/10[a]	Frequency: 1–2 episodes per month: 28%; duration: $\leq$2 hours: 44%, >1 week: 33%	Higher degree of disability related to greater pain intensity ($r = 0.50$) and duration ($r = 0.59$). Pain-related disability in recreation, occupation, social activity, family responsibilities, sexual behaviour, self-care and life-supporting activities.
Koh et al.[3]	46% ($n = 21$)	Chest: 37%; head/neck: 33%; abdomen/pelvis: 50%	1.0/10[b] (median); moderate in 11%	Frequency: daily: 13%, 3–5 times/week: 9%, 2–3 times/week: 13%, weekly: 11%, 1–3 times/month: 22%, <1 month: 33%; duration: <1 h: 65%, few hours: 17%, half day: 7%, all day: 9%	Pain intensity, duration or degree of emotional upset unrelated to disease severity. Those with weekly pain reported more functional limitations ($p < 0.001$). Those with chest pain reported more functional limitations ($p < 0.001$).
Palermo et al.[4]	46% ($n = 21$)	Chest: 37%; head/neck: 33%; abdomen/pelvis: 50%	1.0/10[b] (median)	NR	Those with more frequent pain had reduced vitality ($r = -0.66$), more respiratory ($r = -0.47$) and digestive ($r = -0.50$) symptoms and poorer perception of overall QOL ($r = -0.65$). Those experiencing greater bother from pain and increased frequency had reduced physical function, increased treatment burden, greater role limitations and school performance, reduced perception of their health, poorer respiratory and digestive QOL. Increased number of locations of pain associated with worse physical function ($r = -0.37$). No difference in emotional state, social limitations or body image.
Sawicki et al.[23]	43% ($n = 13$)	NR	Maximum intensity 0.8 (1.4)	NR	NR

(continued)

Table 3. (continued)

Study	Prevalence	Pain regions	Pain intensity	Pain frequency and/or duration	Clinical associations
Flume et al.[24]	64% ($n = 32$)	Back: 25%; chest: 9%; abdomen: 19%; extremities: 6%; head: 34%; neck: 6%	Mean: 4.0 (range 3–10)[a]	NR	Those with pain had worse sleep quality (75.8 vs. 41.2, $p = 0.006$) compared to those without pain. Greater sleep disturbances and daytime dysfunction in those with pain compared to those without ($p = 0.001$). No difference in sleep duration, use of sleeping medication or sleep latency. Strong correlation with pain interference with sleep and global PSQI ($\rho = 0.56$, $p < 0.001$). Those with poorer sleep quality had a higher level of pain interference with sleep, with a strong correlation in pain interfering with frequency of pain interference and severity of sleep abnormality ($p < 0.001$).
Sermet-Gaudelus et al.[25]	Children: 59% ($n = 43$); adults: 89% ($n = 98$)	Children: cervicalgia: 3%, chest: 16%, stomach: 10%, abdomen: 60%, backache: 16%, muscular: 19%, arthralgia: 11%; adults: headache: 35%, cervicalgia: 10%, chest: 26%, stomach: 7%, abdomen: 36%, backache: 50%, muscular pain 6%, arthralgia 20%	Children: maximum intensity 4.9 (2.2)[b]; adults: maximum: 6.0 (2.2)[b]	Children: frequency – 8(9) episodes in last month; duration – mean duration of episode within last month: 7(13) h; adults: frequency – 10(9) episodes within last month; duration – mean duration of episodes 9 (11) hours	Children: 51% of children reported interference of pain with QOL, physical activity for 28% of the children and asthesia for 28%; 13% reported pain affected on school absenteeism, 25% negative impact on family, with 6% reported insomnia with pain. Disease severity unrelated to pain prevalence, intensity, duration or recurrence of episodes. Adults: no difference in pain prevalence, intensity, recurrence or length of episode between those with mild vs. severe disease. Those with more severe disease reported more chest pain (33% vs. 15%, $p = 0.04$). Negative impact on family life in 29%, asthenias in 58%, work absenteeism 21%, limited physical activity 44%, insomnia in 34%, altered quality of life in 70%.

(continued)

Table 3. (continued)

Study	Prevalence	Pain regions	Pain intensity	Pain frequency and/or duration	Clinical associations
Stenekes et al.[6]	84% ($n = 103$)	Headaches: 50%, chest/lungs: 16%, back/spine: 15%, UL/LL: 12%	Headaches 5.2 (2), abdomen 5.3 (2.2), chest and lungs 4.5 (2.1), back/spine 6.9 (1.6), UL/LL 6.5 (1.1)	Duration: headaches <1 year: 16%, 1–2 years: 18%, 3–5 years: 19%, >5 years: 16%	More females with headaches ($p = 0.003$), no difference between children and adults. Both headaches ($r = 0.45$) and abdominal pain ($r = 0.38$) inhibited activity.
Hayes et al.[9]	82% ($n = 68$)	Head: 64%, sinuses: 54%, back: 50%, chest: 46%, abdomen: 34%, knee: 30%, wrist: 19%, fingers: 5%	42% Reported moderate to severe; 33% rating >5/10[a]	Duration: 27% report duration of pain $\geq$6 months	Pain associated with worse respiratory ($p = 0.008$), digestive ($p = 0.01$) and role-related QOL ($p = 0.005$). Pain interfered with general activity, mood, work and was associated with depression ($p = 0.43$) and anxiety ($p = 0.31$). Those with pain had greater pain catastrophizing scores. Those with higher levels of pain were at greater risk of an exacerbation (OR 1.65, $p = 0.04$) and death (HH = 2.28, $p = 0.008$).
Munck et al.[26]	6% ($n = 8$)	Abdomen: 100%, chest: 38%, head: 13%	Ratings of moderate to severe	Duration: 30 minutes to few hours; frequency: 4 days up to 23 days (of 28 days)	Reports of emotional upheaval and anxiety in two patients with pain.
Kelemen et al.[5]	Stable: 89% ($n = 65$) and acute: 79% ($n = 26$)	Stable neck/head: 52%, back/hips/buttocks: 70%, chest: 20%, UL: 23%, LL 27%; acute: neck/head: 50%, back/hips/buttocks: 31%, chest: 35%, UL: 27%, LL: 20%	Stable: average: 2 (1–4), [a]worst: 4 (0–9).[a]; acute: average: 3 (2–5),[a] worst 3 (0–9)[a]	NR	Stable patients reported more interference of pain with exercise than ACT or breathing. Pain also interfered with mood, sleep, enjoyment of life and general activity. Higher pain intensity was associated with poorer QOL for physical function ($p = 0.01$), interference with treatment ($p = 0.03$) and demands of work ($p = 0.02$). Unwell patients reported greater pain interference with ACT and coughing. High pain intensity in acutely unwell patients reported poor physical function ($p = 0.013$) and social aspects of QOL ($p = 0.017$). Pain catastrophizing was associated with higher pain intensity and poorer QOL.

(continued)

Table 3. (continued)

Study	Prevalence	Pain regions	Pain intensity	Pain frequency and/or duration	Clinical associations
Blackwell and Quittner[2]	74.5% ($n = 71$)	Head/neck: 42%; chest: 37%; abdomen: 49%	Average: 2/10	NA	Presence of pain associated with treatment burden ($r = -0.27$), respiratory symptoms ($r = -0.24$), higher levels of depression ($r = 0.29$) and anxiety ($r = 0.28$). Treatment-related pain was of greater intensity than general pain ($p < 0.01$), with ACT most frequent treatment associated with pain. Higher pain intensity, greater number of pain episodes and longer duration was associated with worse QOL, treatment burden and severity of respiratory symptoms (all $p < 0.01$).
Michel-Cherqui et al.[27]	71% ($n = 52$)	Back: 34%, head: 34%, joint: 34%, chest: 28%, abdomen: 19%, limb: 19%	NR	NR	Neuropathic pain found in 6% of participants, with no difference in frequency compared to those with other respiratory conditions ($p = 0.67$).

ACT: airway clearance therapy; NR : not reported; *r*: Pearson's correlation coefficient; QOL: quality of life; PSQI: Pittsburgh Sleep Quality index; UL/LL: upper limb/lower limb; VAS: visual analogue scale; NRS: numerical rating scale.
[b]VAS.
[a]NRS.

with absence from work or study.[20,24] It negatively influenced sleep[5,21,24,25] and was associated with heightened psychological symptoms of anxiety and depression[9,24] and pain catastrophizing.[5,9] No studies reported on the relationship between pain and other co-morbidities.

Of those studies which described treatment strategies implemented, medical approaches included analgesics (ranging from acetaminophen, non-steroidal anti-inflammatory agents, aspirin and hydrocodone) in both children and adults.[2,3,6,21,25] Non-pharmacological approaches which included massage,[21,25] acupuncture,[21,25] osteopathy and homeopathic agents,[21,25] rest and relaxation,[3,21] heat and ice therapy[3] and physical activity[21] were also prescribed.

Phase 2 – Instrument measurement properties

A total of 348 studies were retrieved. Following duplicate removal, 39 studies were reviewed, with 5 meeting the inclusion criteria, all of which were included in phase 1.[2,5,9,20,24] The measurement properties for the three identified instruments are summarized in online Supplemental data 3 and included construct validity/hypothesis testing and criterion-predictive validity. Overall, the studies scored 'good' or 'fair' for the measurement properties evaluated. The poorest scoring areas were design requirements (lack of a prior hypotheses, sample size and absence of expected direction of correlations or differences).

Measurement properties. The measurement properties established for instruments applied in CF are outlined in online Supplemental data 3. For criterion-predictive validity of the BPI, increased pain intensity was found to be associated with a 65% increased risk of acute exacerbations and twofold increase in mortality.[7] For construct validity of the BPI, whilst there was no relationship to disease severity,[26] pain prevalence overall and specifically back or chest pain was significantly related to HRQOL pertinent to symptoms, physical role and a greater degree of pain catastrophizing.[9] Pain interference was moderately linked to sleep quality.[24] Pain intensity was moderately associated with pain catastrophizing and interference with physiotherapy treatments, respiratory symptoms and HRQOL.[5] For the MPI, a weak relationship was evident between measures of disease severity and pain.[20] For the Daily Pain Assessment Questionnaire for CF (DPAQ-CF), pain characteristics had a weak relationship with QOL domains and psychological symptoms and a significant association with treatment burden and respiratory symptoms.[2]

Discussion

Both children and adults with CF experience a high prevalence of musculoskeletal pain (74%), greater than that reported in comparative healthy controls. Whilst the experience of pain appears to be unrelated to disease severity, the duration and frequency of pain experiences are variable. Clinically, pain experiences have a negative influence on respiratory symptoms and HRQOL, including interfering with the ability to undertake usual treatments. There was insufficient information to establish the measurement properties of the instruments used in CF, with the evidence rated as fair to good.

Some degree of heterogeneity in the prevalence of pain was evident in both the children and adult populations. This is likely to be attributable to the differing methods of population sampling; the mix of both adults and children in some studies[6,25] and the use of convenience sampling and self-selection in some studies may introduce some bias. The differing sample sizes between studies may also be a factor. Despite this, it is apparent that pain is a co-morbidity across the lifespan, with high levels reported in individuals hospitalized for an acute exacerbation of CF as well as a stable clinical state.[5] It also appears to be a concurrent problem across different degrees of disease severity,[5,25] although this should be confirmed with further studies.

The intensity of pain ranged from mild to severe,[2,3,5,6,9,18, 20–22,24,25,27] and was unrelated to the age of the population studied or disease severity. The reporting of pain severity is influenced by several factors, including the individual tolerance of symptoms. With continual respiratory symptoms of chronic cough, sputum production and dyspnoea, it is possible that a high pain threshold is present in some individuals. However, with not all studies reporting pain levels at its worst,[5,6,18,21,25] this is difficult to accurately determine. The variable method of reporting the duration of pain experiences from isolated episodes,[3,18,21,22] to the overall length of time over which pain has been experienced,[6,9] increases the difficulty in defining the precise duration of this clinical feature. Although selected studies defined chronic pain[6,9,25] based on the recognized definition of any

pain lasting more than 12 weeks,[28] further examination of this specific characteristic would assist in clarifying the chronicity of pain in CF. With studies identifying acute causes of pain related to physiotherapy and medical procedures in the current review,[2,3] the underlying mechanism behind pain is likely to differ to that of chronic pain experiences. As this will influence treatment options, it is important to distinguish between acute and chronic causes.

A number of possible aetiologies of pain in CF have been proposed. Potential sources of abdominal pain in CF include gastro-oesophageal reflux disease, pancreatitis, liver and biliary disease, constipation and intestinal obstruction.[29] Within this review, among those with more severe disease, specific reasons accounting for back, chest and limb pain included orthopaedic causes or secondary complications were described.[19] Common orthopaedic complications of CF are osteoporosis with associated rib and vertebral fractures[30] as well as CF-related arthropathy.[31] More recently, postural abnormalities incorporating increased thoracic kyphosis, with associated muscle weakness, soft tissue contractures and spinal deformities have been reported [32,33] and may account for some regions of pain described in this review. This suggests the need for further study examining the link between pain experiences and postural changes in individuals with CF.

The interference of pain with not only respiratory symptoms[2,4,5,7,17] but the ability to successfully undertake treatment, including physiotherapy airway clearance techniques and exercise,[2,5,18,21] is a significant clinical concern. This is illustrated by the evidence from one study that pain during physiotherapy treatment was found to promote the risk of future exacerbations.[9] Physiotherapy is the cornerstone of CF management[1,34,35]; factors that limit effective completion of and adherence to physiotherapy are critical to identify. This is illustrated by the evidence from one study that pain during physiotherapy treatment was found to promote the risk of future exacerbations.[9] Similarly, the negative association with daily activities, sleep and HRQOL further highlights the clinical importance of pain. Together with heightened anxiety and depression in those with pain,[2,9,26] and pain catastrophizing,[5,9] this highlights the value in screening for pain.[35] The ever improving survival rates in CF[36] imply that this complication may rise in prevalence; gaining thorough knowledge of the implications of pain could facilitate clinical care.

A variety of treatment options have been suggested to tackle pain in CF, including pharmacological (analgesics) and non-pharmacological options.[2,3,19,21,25,27,37] Current guidelines have suggested that efforts to minimize some causes of pain are within the scope of physiotherapy practice, which may include physical modalities.[1,35] Whilst this may incorporate manual treatment and exercises for optimal posture, mobility and muscle function,[1,32,38–40] options (including the use of heat and ice) and psychological interventions (distraction, relaxation, mindfulness and counselling) are also warranted. Further study is required to determine the most effective treatment strategies.

The heterogeneity of disease severity between studies in both children and adults makes interpretation of the results difficult. Whilst most focused including individuals in a clinically stable state, disease severity remained variable across studies. This together with the absence of sample size calculations suggests that the ability to generalize these findings, particularly those pertaining to the clinical implications of pain to the broader CF population may be limited. The inconsistent use of valid or reliable questionnaires for assessing pain in this population may question the accuracy of pain experiences reported.

This is the first review examining the measurement properties of questionnaires formally assessing pain in CF. The assessment burden of the three questionnaires is low, making any a practical choice. However, a maximum of two measurement properties have been established for each questionnaire and the overall quality of studies ranged from fair to good. Due to the different comprehension of pain and its impact on activities and HRQOL, it is likely that different but validated questionnaires would be applied in children compared to adults with CF. This approach would ensure maximal clarity of understanding with age-appropriate options for assessing interference and impact of pain are applied to all individuals with CF. The comprehensive nature of DPAQ-CF which is specifically designed for CF could be considered. Conversely, the BPI has been more widely used within this population.[5,9,21] With both tools requiring further validation and identification of reliability, at present, either tool may be the suitable choice until further research is completed.

This review has limitations, with some studies not differentiating between pain in children and adults, which limited their inclusion within the pooled prevalence analysis. Although the COSMIN scoring

system is designed to evaluate studies on measurement properties, no study included in this review had this as its primary aim, which may influence the low COSMIN scores observed.

In conclusion, this review illustrates that pain appears to be a common problem in individuals with CF. The associations between pain and HRQOL, and its degree of interference with treatment, including physiotherapy interventions implies that this comorbidity has important clinical consequences. Due to the different implications for treatment, further work is required to distinguish between acute pain experiences and those relating to chronic pain. Greater exploration of individual experiences of pain through qualitative studies is warranted. There is limited information regarding the properties of current pain outcome measures. Validated and age-appropriate questionnaires should be applied across the lifespan to ensure an accurate reflection of pain experiences is obtained from both children and adults. Further work to establish other measurement properties of the BPI and DPAQ-CF, including additional measures of validity, reliability and responsiveness to treatment would be of value to clinicians.

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Supplemental material

The online [appendices/data supplements/etc] are available at http://crd.sagepub.com/supplemental.

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