Review Article

The interplay of physical and cognitive function in rehabilitation of interstitial lung disease patients: a narrative review

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Background and Objective: Interstitial lung disease (ILD) encompasses several diverse pulmonary pathologies that result in abnormal diffuse parenchymal changes. When prescribing rehabilitation, several additional factors need to be considered as a result of aging, polypharmacy, and comorbidities manifested in ILD patients. This review aims to discuss issues related to frailty, skeletal muscle and cognitive function that limit physical activities in ILD patients. It will also highlight exercise training and propose complementary strategies for pulmonary rehabilitation.

Methods: A literature search was performed in MEDLINE, CINAHL (inception to October 19th, 2022) using search terms based on concepts of: idiopathic pulmonary fibrosis or interstitial lung disease; frailty; muscular atrophy; skeletal muscle dysfunction; cognitive dysfunction; sleep quality; sleep disorders; anxiety disorders; or depressive disorders. After eligible texts were screened, additional references were included from references cited in the screened articles.

Key Content and Findings: Frailty and skeletal muscle dysfunction are common in ILD. Weight loss, exhaustion, and anti-fibrotic medications can impact frailty, whereas physical inactivity, aging, corticosteroids and hypoxemia can contribute to sarcopenia (loss of muscle mass and function). Frailty is associated with worse clinical status, exercise intolerance, skeletal muscle dysfunction, and decreased quality of life in ILD. Sarcopenia appears to influence wellbeing and can potentially affect overall physical conditioning, cognitive function and the progression of ILD. Optimal assessment tools and effective strategies to prevent and counter frailty and sarcopenia need to be determined in ILD patients. Even though cognitive impairment is evident in ILD, its prevalence and underlying neurobiological model of contributing factors (i.e.,

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inflammation, disease severity, cardiopulmonary status) requires further investigation. How ILD affects cognitive interference, motor control and consequently physical daily activities is not well defined. Strategies such as pulmonary rehabilitation, which primarily focuses on strength and aerobic conditioning have demonstrated improvements in ILD patient outcomes. Future incorporation of interval training and the integration of motor learning could improve transfer of rehabilitation strategies to daily activities.

Conclusions: Numerous underlying etiologies of ILD contribute to frailty, skeletal muscle and cognitive function, but their respective neurobiologic mechanisms require further investigation. Exercise training increases physical measures, but complementary approaches may improve their applicability to improve daily activities.

Keywords: Lung diseases; interstitial; frailty; sarcopenia; cognitive dysfunction

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Introduction

Interstitial lung disease (ILD) is an umbrella term for diseases with abnormal diffuse parenchymal lung changes. ILDs can be due to identifiable causes, such as occupational or environmental inhalation exposures, familial, connective tissue diseases, and drugs. They can also arise from unknown causes, known as idiopathic interstitial pneumonias. The clinical presentation and prevalence of these phenotypes are heterogenous (1). The clinical course of the different ILD ranges from completely reversible to self-limiting to progressive and can be fatal despite optimal management. Globally, ILDs have a reported incidence ranging from 1 to 31.5 per 100,000 person-years and prevalence ranging from 6.3 to 71 per 100,000 people (2).

Antifibrotic therapies for ILD have improved, which in turn have offset lung function decline and extended life expectancy (3-5). Complex medication regimens with immunosuppressive medications are common in ILD patients with different aetiologies resulting in a high frequency of potential drug–disease interactions (6). However, these treatments together with longevity have presented an increasing number of adverse effects from polypharmacy (7,8). Although antifibrotic therapies aim to slow disease progression, to date, reduction in symptoms or improvement in activities of daily living (ADL) and health-related quality of life (HRQL) have not been shown (7).

Aging results in progressive physiologic alterations of several bodily systems that can compound changes due to chronic respiratory diseases such as ILD (9). Although 60% to 70% of idiopathic pulmonary fibrosis (IPF) patients die as a consequence of an exacerbation, other causes of death can result from comorbidities related to aging, lifestyle, and disease progression (i.e., lung cancer, cardiovascular diseases, and pulmonary hypertension) (10). Across several studies, frailty is highly prevalent in ILD patients (4,11-13). An increasing number of reports have documented sarcopenia (loss of muscle mass and function) in ILD (13-15), which may be more evident in aging populations (16) and importantly, a risk factor for pending frailty (17,18). Frailty and sarcopenia are associated with increased adverse outcomes including falls, functional declines, and mortality (19-21). Hence, maintaining muscle mass and muscle strength are key elements to preventing muscle dysfunction in ILD (12) and related comorbidities (22,23).

Dyspnea, a highly prevalent symptom in ILD patients has been attributed to ventilatory limitation resulting from decreased lung compliance and gas exchange impairment (24). Dyspnea is considered to contribute to decreased ADL, HRQL, exercise capacity, and physical inactivity in ILD. However, dyspnea may not only limit physical activity but also unduly load cognitive demands. Increased ventilatory demands associated with dyspnea require conscious efforts and cortical activation (25), which may limit cognitive capacity for other tasks. Through similar processes, dyspnea may limit ILD patients via its affective sensation and by limiting the available cognitive capacity (i.e., concentration, memory, and executive function) for well-coordinated purposeful movement (26).

Due to the increasing median age of ILD patients, several new considerations for rehabilitation arise as a result of aging, polypharmacy, and comorbidities (4). Aging-related syndromes such as sarcopenia and frailty

Table 1 The search strategy summary

Items	Specification
Date of search	19 October 2022
Databases and other sources searched	Ovid Medline, CINAHL Ultimate (EBSCOhost)
Search terms used	exp lung diseases, interstitial/
	Frailty/
	exp muscular atrophy/
	(Skeletal muscle* adj2 dysfunction*).mp.
	Cognition disorders/ or exp cognitive dysfunction/
	Sleep/ or sleep quality/
	exp sleep wake disorders/
	exp anxiety disorders/
	exp depressive disorder/
	exp anxiety/
	Depression/
Timeframe	1946–2022
Inclusion and exclusion criteria	English and Japanese language
Selection process	MH, TT, RK, AOC, DR, and WDR conducted the selection, and obtained consensus

are recognized as contributors to physical impairments in ILD, and daily activities may be further limited by cognitive interference and impairments. This review aims to discuss the multifaceted issues related to physical and cognitive function that limit physical activities in ILD patients and provide potential new directions for pulmonary rehabilitation. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-209/rc).

Methods

The search strategy was developed with the assistance of a reference librarian (AO-C) (*Table 1*) (27). Ovid MEDLINE and EBSCO CINAHL Ultimate databases were searched from inception to October 19th 2022 using search terms based on concepts of: interstitial lung diseases, frailty, muscular atrophy, skeletal muscle dysfunction, cognitive dysfunction, sleep quality, sleep disorders, anxiety disorders, or depressive disorders. The search was limited to human studies and full-text articles in English or Japanese (Appendix 1). After eligible texts were screened, additional references were included from references cited in the screened articles.

Main findings—physical and cognitive limitations in ILD patients and related evaluations

The main findings of this review describe the multifaceted issues related to physical and cognitive function in ILD patients (*Figure 1*). Examination of frailty in ILD provides an underlying construct to further describe physical and cognitive limitations. Moreover, how the exercise training in pulmonary rehabilitation can be complemented through a cognitive or motor control lens is proposed. The main findings will describe: (I) frailty in ILD; (II) skeletal muscle dysfunction in ILD; (III) cognitive limitations in ILD; (IV) exercise training in pulmonary rehabilitation for ILD patients.

Frailty in ILD

Previous studies reported the prevalence of frailty in ILD patients to range from approximately 24% to 55% (*Table 2*). However, the evidence of frailty in ILD patients is not well-

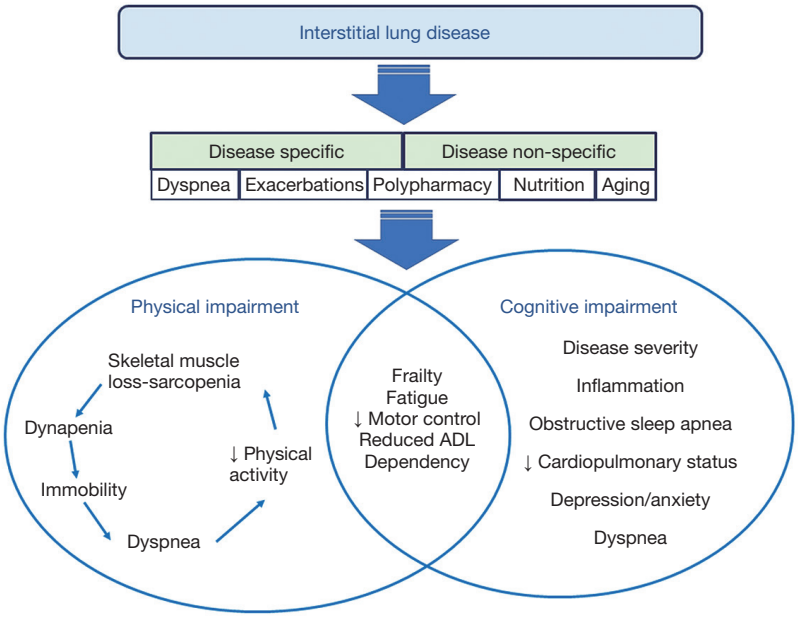

Figure 1 Physical and cognitive limitations in interstitial lung disease patients. ADL, activities of daily living; ↓, decreased.

described. Detailed mechanisms contributing to frailty are not completely understood and the optimal assessment tool for frailty in ILD patients remains to be defined. Moreover, ILD patients with frailty have decreased activity levels, and hence, maintenance of physical activity is essential to mitigate frailty. This section will define frailty, describe the three most common frailty models utilized in the chronic lung disease literature, and highlight the clinical implications of frailty in ILD.

Definition of frailty

The concept of frailty is a disorder of multiple interrelated physiological systems and is considered to be distinct from the functional losses associated with physiological aging and comorbidities (35,36). A consensus group consisting of six international societies defined physical frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (37). Despite the work by consensus groups globally, a gold standard definition of frailty remains to be defined, especially in the ILD population (37-39). To date, no specific treatment for frailty has been proposed, other than modifying a sedentary lifestyle and nutritional factors (35,40). However, it is considered that early intervention has the potential to mitigate frailty, improve HRQL and reduce health care costs (37).

Frailty assessments have shown that both physical and cumulative deficits contribute to this syndrome (41). The main models of frailty are: (I) the physical frailty model, also indicated as phenotypic or syndromic frailty, and (II) the cumulative deficit frailty model, which captures the deficits in physical and psychosocial elements in an individual. Frailty assessments are meant to capture inter-related measures that are known to be predictive of clinical outcomes, through assessments of physical function, sarcopenia, cognitive and psychological assessments, nutritional state, and immunologic alterations (42).

Frailty scales

A number of frailty scales have been developed to identify varying degrees of physical, psychological, or social function, with 67 frailty scales applied to community-dwelling populations based on a 2016 report (43). Three scales appear to be used most often in chronic lung disease and may be suitable to evaluate ILD patients. The Fried Frailty Phenotype (FFP) index (44) is the most common frailty index utilized to date and proposes five components (weakness; slowness; unintentional weight loss; exhaustion and low physical activity). Patients who have three or more criteria are classified as frail. In contrast, the cumulative deficits model evaluates frailty based on an accumulation of health deficits (symptoms, laboratory measures, disabilities,

Table 2 Frailty in interstitial lung disease

Author, year, country	Age, years	Sex (M:F)	Diagnosis	Prevalence of frailty, %	Clinical outcomes
Fried frailty phenotype					
Montgomery *et al.* (28), 2022, Australia	55	49%:51%	Patients listed for lung transplant; ILD (n=130)	44	The addition of cognition and depression to assessment of physical function increased number classified as frail, but these measures did not change the strength of association with lung transplant waitlist mortality
Farooqi *et al.* (18), 2021, Canada	68	55%:45%	ILD (n=463): IPF 183, CTD-ILD 79, HP 27, sarcoidosis 22, other 152	26	Frailty was independently associated with an increased risk of death
Montgomery *et al.* (29), 2020, Australia	57	71%:29%	ILD (n=100): IPF 68, HP 11, NSIP 3, CTD-ILD 7, other 11	24	Frailty was associated with anemia, hypoalbuminemia, and the need for supplemental oxygen
Sheth *et al.* (30), 2019, USA	76	58%:42%	IPF (n=48)	48	Factors related to frailty were aging, lower FVC, DLco, 6MWD, severe fatigue and dyspnea, and increased comorbidities
Rozenberg *et al.* (31), 2018, Canada	59	58%:42%	ILD (n=34)	26	Frailty had moderate correlations with 6MWD, short physical performance battery, and activities of daily living
Singer *et al.* (32), 2015, USA	58[†]	51%:49%[†]	Patients listed for lung transplant; ILD (n=208)	29	Frailty is independently associated with greater disability and an increased risk of delisting or death pre-transplant
Cumulative deficit scales					
Guler *et al.* (33), 2020, Canada	M: 67, F: 63	43%:57%	Fibrotic ILDs (n=540): IPF 100	50	Functional ageing is associated with adverse health outcomes (quality of life, hospitalizations and survival)
Milne *et al.* (4), 2017, Canada	69	54%:46%	ILD (n=129): IPF 41	50	Dyspnea severity is independently associated with frailty and a more important determinant of frailty than pulmonary function
Guler *et al.* (34), 2017, Canada	61	20%:80%	Systemic sclerosis associated ILD (n=86) and CTD-ILD (n=167)	55	Dyspnea is strongly associated with frailty

[†], data for the entire cohort, not specifically the ILD subgroup. No studies were found that applied the Clinical Frailty Scale. M, males; F, females; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; HP, hypersensitivity pneumonitis; CTD-ILD, connective tissue disease - associated interstitial lung disease; NSIP, nonspecific interstitial pneumonia; FVC, forced vital capacity; DLco, diffusing capacity of lung for carbon monoxide; 6MWD, six-minute walking distance.

and comorbidities), and captures physical, psychological, and social function (45,46). Increased frailty based on accumulation of deficits has been shown to be associated with adverse clinical outcomes in a diverse group of patient populations including community dwelling older adults, solid organ transplant populations, and chronic disease states (47-50). A third scale, the clinical frailty scale evaluates the overall level of frailty and fitness (51) and consists of specific domains: comorbidity, function, and cognition. This scale provides a score ranging from 1 (very fit) to 9 (terminally ill) (51) and a higher score has been associated with worse clinical outcomes in community dwelling adults and individuals with chronic obstructive pulmonary disease (COPD) (i.e., increased mortality and admission to an institution) (52). The clinical frailty scale has not been applied to-date in ILD patients but may offer a complementary measure of frailty in ILD patients in the clinical setting. To-date, only the Fried and

cumulative deficits scales have been utilized in ILD patients (*Table 2*), and the most sensitive and responsive measure in ILD remains to be determined (33).

Frailty in ILD patients and its clinical implications

Several studies reported evidence of frailty in ILD patients (*Table 2*). The prevalence of frailty ranged from 24% to 48% when the Fried scale was applied to patients in three different countries (Australia, Canada, and USA) (*Table 2*) (18,28-32,53). The prevalence was higher in the three studies that utilized the cumulative deficits index ranging from 50 to 55% (4,34,54).

Across several ILD studies using the Fried and cumulative deficits scales (*Table 2*), frailty was commonly associated with increased ILD disease severity (lung function, supplemental oxygen, and six-minute walking distance (6MWD) (29-32). Frailty may predict medication side effects (33) and has been shown to be associated with a significantly higher prevalence of depressive symptoms in ILD patients (55). Furthermore, arthropathy was common in connective tissue associated ILD and may have a profound impact on functional mobility and physical activity levels. Thus, patients with connective tissue disease-associated ILD were more likely to be frail than non-frail (56). Several studies utilizing the cumulative frailty index demonstrated that dyspnea was a stronger determinant of frailty than measures of lung function (4,34). Importantly, frailty was associated with an increased risk of hospitalizations, worse HRQL and higher risk of delisting while awaiting lung transplantation. In addition, frail patients were shown to have three times higher risk of mortality (29,32,54). Another report corroborated this finding and showed that frailty was predictive of mortality, independent of age, sex, lung function, and underlying ILD diagnosis (18).

Summary of frailty

Detailed mechanisms contributing to frailty remain to be determined but it is considered to be a common risk factor for adverse outcomes in ILD patients. Frailty domains such as weight loss and exhaustion could be influenced by medications (steroid or anti-fibrotic use) and their interactions (18). Frailty appears to be associated with worse clinical status, exercise intolerance, skeletal muscle dysfunction, and decreased HRQL in ILD. Further studies are needed to determine the optimal assessment tools and to develop multifaceted strategies to prevent and counter frailty in ILD patients (34,54).

Skeletal muscle limitations in ILD

Multiple factors have been shown to contribute to skeletal muscle dysfunction in ILD patients. Most investigations have examined limb muscles (57,58), however, respiratory muscle dysfunction has been considered because it can also impact the progression to respiratory failure (59). This section will describe issues of limb muscle dysfunction related to loss of muscle mass and function, along with several sarcopenia definitions. Risk factors for skeletal muscle dysfunction such as corticosteroids, physical inactivity, aging, and hypoxemia will be briefly discussed. The literature on respiratory muscle dysfunction will also be synthesized.

Limb muscle dysfunction and its associated risk factors

Multiple factors contribute to skeletal muscle loss in chronic lung disease, including but not limited to disease progression, physical inactivity, and corticosteroid use (60). Skeletal muscle dysfunction in ILD patients has received increased attention more recently and has important implications on daily function (58,61,62). In addition to skeletal muscle dysfunction, other contributing factors limiting daily function include: dyspnea, hypoxemia, poor sleep, comorbidities, and psychological stressors (63), which can in turn exacerbate skeletal muscle dysfunction. Although anti-fibrotic therapy may slow lung function loss, IPF patients receiving this therapy appear to have ongoing skeletal muscle loss, where skeletal muscle mass has been shown to be an important prognostic marker of survival (12). Moreover, ILDs other than IPF are treated with systemic corticosteroids and immunosuppressive therapies (64,65) that can contribute to skeletal muscle dysfunction through various side effects. This is considered to occur due to increased muscle proteolysis and decreased protein synthesis (66,67) which contributes to muscle atrophy, decreased muscle fiber size and corresponding skeletal muscle weakness (68-70). This can be increasingly exacerbated by long-term corticosteroid treatment in ILD patients (57). Corticosteroid treatment has been associated with skeletal muscle weakness, even in those with mild dyspnea (71), highlighting the importance of early intervention in ILD through exercise and physical activity to counter skeletal muscle dysfunction.

Skeletal muscle dysfunction is often considered a part of the common diagnostic criteria for frailty (72) through interrelated factors such as muscle weakness, physical inactivity and weight loss, which are often associated with

muscle wasting. In addition, the common symptoms of fatigue and dyspnea in ILD can lead to a perpetuating downward spiral of physical inactivity and can accentuate deconditioning. Increased fatigue has an important impact on ADL and physical activity levels, independent of age and disease severity, and frailty encompasses other elements beyond skeletal muscle and physical function such as psychosocial function.

Physical activity in ILD patients

Physical activity is one of the most important factors in mitigating frailty and skeletal muscle dysfunction. Wallaert *et al.* (73) showed that IPF patients walked 65% fewer daily steps compared to the healthy sedentary control group. Additionally, ILD patients with greater impairments in physiological function had lower physical activity levels and demonstrated greater sedentary behaviors (74). In lung transplant candidates with severe ILD, quadriceps strength demonstrated a moderate correlation with total daily step count, whereas no significant correlation with lung function was observed (75).

Physical inactivity may contribute to skeletal muscle deconditioning and a cycle of decreased physical fitness and exercise intolerance (76,77). In particular, daily steps count in ILD patients showed that fewer than 3,300 daily steps was associated with an increased risk of mortality (73,78,79). However, other studies observed no associations between baseline daily steps count or its association with 12-month survival (80,81). Thus, unlike the association of physical inactivity with skeletal muscle dysfunction in ILD, the association between daily step count and prognosis in ILD patients requires further characterization.

Sarcopenia in ILD

Sarcopenia has been defined as a systemic, progressive skeletal muscle decline that involves the loss of muscle mass and function and is associated with adverse outcomes including falls, functional decline, frailty, and mortality in community dwelling populations (19,82). The definitions for sarcopenia have been variable with both the 2019 European Working Group on Sarcopenia in Older People 2 (EWGSOP2) (82) and the Sarcopenia Definitions and Outcomes Consortium (SDOC) (83) utilizing low muscle strength as a primary criterion. However, EWGSOP2 also added the criterion of low muscle mass whereas SDOC also requires low gait speed. In Asia, the Asian Working Group for Sarcopenia (AWGS) 2019 consensus (84) is often utilized, which requires low muscle mass and one of either low strength or physical performance.

Only a few studies have provided evidence of sarcopenia in ILD patients (*Table 3*). According to EWGSOP2 definition (82), sarcopenia was identified in 19 (22.9%) IPF patients, in a cohort of consecutive patients followed in 9 hospitals across Italy (14). Using the AWGS 2019 criteria (84), sarcopenia was identified in 32.1% ILD patients (13) and 39.3% in IPF patients (15) living in Japan. Given the variability in diagnostic criteria for sarcopenia, comparisons between studies are often challenging among cohorts. The following sections highlight studies that assessed skeletal muscle mass, strength or function, which are key elements comprising sarcopenia.

Assessment of skeletal muscle mass

Reports utilizing the sarcopenia criteria in ILD have been limited (82,84). Skeletal muscle mass in ILD has often been quantified using the cross-sectional area of thoraco-abdominal muscles measured from computed tomography (CT) (90). Studies have shown that decreased cross-sectional areas of erector spinae muscles (ESMCSA) (91,92) and pectoralis muscles (PM CSA) (62,93) measured with CT images were associated with lower skeletal muscle mass index, decreased quadriceps strength, increased ILD severity (11,93-95) and mortality (93). Future evaluation of low muscle mass may be informative through more accessible modalities such as body composition with dual-energy X-ray absorptiometry (DXA) (86) or bioelectrical impedance analysis (BIA) (96).

Assessment of skeletal muscle strength and function

Skeletal muscle strength, specifically quadriceps strength, has been shown to be reduced in ILD in several studies, as shown in *Table 3* (58,87,88). Mendoza *et al.* demonstrated with non-volitional tests that quadriceps strength and endurance were significantly lower in fibrotic ILD patients than community healthy controls (87). Furthermore, quadriceps force was observed to be lower in IPF patients compared to COPD prior to rehabilitation, which may help explain part of the variable response with pulmonary rehabilitation between the two disease states (76). Quadriceps strength has been shown to be an important determinant of exercise capacity (75,87,89), including post-rehabilitation (76).

The exact contribution of disease severity and lung function on muscle strength remains unclear, as some studies have suggested a positive association (88,89), whereas others have demonstrated no correlation (75).

Table 3 Limb muscle dysfunction in interstitial lung disease

Author, year, country	Age, sex (M:F)	Diagnosis, n	Definition criteria	Prevalence of sarcopenia	GAP score	BMI, kg/m^2	%FVC, %	Muscle mass		Strength/function	
								Modality	Reduction in size	Muscle group/function	Comment
Hanada *et al.* (13), 2022, Japan	71 [67–77] years, 65%:35%	ILD, 78	AWGS 2019	32.1%	3 [2–4]	23 [20–28]	85 [63–93]	SMI: 7 [5–7] cm; calf circumference: 33 [30–37] cm	No significant difference compared to non-sarcopenia	QF: 23 [16–33] kgf; HF: 23 [19–33] kgf	No significant difference compared to non-sarcopenia
Fujita *et al.* (15), 2022, Japan	73.1±7.7 years, 88%:12%	IPF, 56	AWGS 2019	39.3%	4 [3–5]	20.7±2.8	74.6±14.8	ASMI: M 6.2 [6.0–6.5] cm; F 5.1 [5.0–5.2] cm	Significantly lower in sarcopenic males compared to non-sarcopenia males	HF: M 26.1 [23.0–28.5] kg, F 15.8 [13.8–16.4] kg; gait speed: 0.8±0.2 m/s	HF significantly lower in males compared to non-sarcopenic male group; no significant difference compared to non-sarcopenic group in gait speed
Wickerson *et al.* (85), 2020, Canada	Mild ILD: 60±9 years, 60%:40%; severe ILD: 65±5 years, 62%:38%	Mild ILD (n=10): IPF 3, other 7; severe ILD (n=13): IPF 4, other 9	NA	NA	NA	Mild ILD, 27±4; severe ILD, 26±3	Mild ILD, 81±17; severe ILD, 59±20	NA	NA	Knee-extensor peak torque: mild ILD 137±44 N·m, severe ILD 104±32 N·m; elbow-flexor peak torque: mild ILD 57±18 N·m, severe ILD 40±18 N·m	No significant difference compared to healthy group (n=13) as well as between mild and severe ILD in knee-extensor or elbow-flexor peak torque; no significant difference between mild and severe ILD in knee-extensor or elbow-flexor peak torque
Guler *et al.* (86), 2019, Canada	M: 69±10 years, F: 66±9 years; 64%:36%	ILD (n=115): IPF 40, other: 75	NA	NA	NA	M: 28±4; F: 28±6	M: 77±17; F: 72±22	SMI: M 7.9±0.9 kg/m^2, F 6.2±1.0 kg/m^2; ALM: M 24.0±3.7 kg, F 16.2±2.6 kg; body fat: M 29.1%±5.2%, F 39.8%±6.5%	Significantly lower muscle mass and higher fat mass in individuals with more impaired pulmonary function	HF: M 40.2±9.6 kg, F 25.6±5.7 kg; 4MGS: M 1.33±0.3 m/s, F 1.25±0.3 m/s	Males with ILD had a weaker HF compared to an age-matched healthy Canadian, although HF was not lower than expected in females with ILD; 4MGS was similar to the general population
Mendes *et al.* (58), 2015, Canada	61±8 years; 73%:27%	IPF: 23; other: 3	NA	NA	NA	27±3	49±13	Rectus femoris CSA, 7.6±2.1 cm; gastrocnemius and soleus layer thickness, 2.8±0.6 cm; biceps layer thickness, 2.6±0.4 cm	Significantly smaller muscle size than community adults	Knee extension peak torque, 119±35 N·m; Ankle plantarflexion peak torque, 37±19 N·m; Biceps brachii peak torque, 39±19 N·m	Leg muscle strength is lower than community adults
Mendoza *et al.* (87), 2014, Chili	64.4±7.7 years; 92%:8%	IPF: 15; unclassifiable ILD: 10	NA	NA	NA	28.6±4.7	78.7±14.0	FFM, 59.5±10.3 kg; %Fat: 30.5±5.4	NS	TwQ: 8.0±2.4 kg	QF is lower than local community participants.
Watanabe *et al.* (88), 2013, Japan	M: 62 [36–69] years, F: 59 [34–75] years; 30%:70%	f-NSIP: 30	NA	NA	NA	NA	%VC, M: 87.5 [57.1–110.6], F: 71.7 [41.7–100.0]	NA	NA	QF: M 148.5 [77.5–236] N·m, F 74.5 [45–110] N·m; HF: M 39.3 [32.5–49.5] kg, F 22.3 [10–36.5] kg	Significantly decreased QF in 16 subjects; both QF and HF were significantly higher in male than in female
Wickerson *et al.* (75), 2013, Canada	62 [53–65] years	IPF: 12; other: 12	NA	NA	NA	25.5±3.5	48.9±14	NA	NA	QT, 120±36 N·m	QT was moderately correlated with daily steps
Kozu *et al.* (76), 2011, Japan	67.5±7.8 years	IPF: 45	NA	NA	NA	21.2±3.3	80.1±17.3	NA	NA	QF, 19.1±10.1 kg; HF, 23.2±9.1 kg	No significant difference compared to COPD group
Nishiyama *et al.* (89), 2005, Japan	64±9 years, 85%:15%	IPF: 41	NA	NA	NA	NA	%VC, 76.6±16.8	NA	NA	QF: 87±28 N; HF: 32±19 N	QF was significantly related to VO_2 max

Data are presented as mean ± standard deviation, median [interquartile range], or numbers (%). M, male; F, female; GAP score, Gender, age, and lung physiology score; BMI, body mass index; ILD, interstitial lung disease; AWGS 2019, the Asian Working Group for Sarcopenia 2019 consensus; SMI, skeletal muscle index; ASMI, appendicular skeletal muscle index; QF, quadriceps force; HF, hand grip force; IPF, idiopathic pulmonary fibrosis; ALM, appendicular lean mass; 4MGS, 4 meter gait speed test; CSA, cross-sectional area; FFM, fat-free mass; TwQ, quadriceps twitch force in response to magnetic femoral nerve stimulation; COPD, chronic obstructive pulmonary disease; f-NSIP, fibrotic- non-specific interstitial pneumonia; QT, quadriceps torque; FVC, forced vital capacity; NSIP, non-specific interstitial pneumonia; N, number of patients; VC, vital capacity; VO_2, oxygen consumption.

There have been no studies to our knowledge that have demonstrated the contribution of skeletal muscle strength or function on ILD survival. Thus, further exploration of skeletal muscle function with disease severity and clinical outcomes remains to be investigated.

Respiratory muscle function

Respiratory muscles in ILD patients have been investigated in several studies with smaller sample sizes that show disparate outcomes. During the early phases of ILD, in spite of increased work of breathing, it is considered that the respiratory muscles are generally preserved. Unlike COPD, the chest wall and diaphragm curvature are altered to a lesser extent which appears to allow diaphragm dependency during tidal ventilation (61). Although preservation of maximal inspiratory pressures (MIP) has been reported in some investigations (61,97), several decrements have been shown including: reduced MIP (98), a greater neural drive (97,98), and reduced non-volitional diaphragm force (97). Further, diaphragm thickening fraction and mobility, visualized using ultrasound, were lower in ILD patients and these impairments were associated with disease severity as determined by forced vital capacity (FVC) percent predicted (99). Moreover, as IPF progresses to advanced stages, hypercapnia may be indicative of ventilatory failure (i.e., respiratory muscles are unable to meet the ventilatory demands) (100).

ILD associated with systemic inflammatory conditions may present with additive atrophic or myopathic changes that compound respiratory muscle impairment. A 3-year study on a cohort of 36 patients with systemic sclerosis-associated ILD showed progressive atrophy of chest wall musculature (i.e., latissimus dorsi muscle, erector spinae muscle, serratus anterior muscle, inferior trapezius muscle, and inferior pectoralis major muscle) (101). Hence, respiratory muscle atrophy in some ILD may be an independent contributor to FVC decline given their major role in forced expiration (102). Taken together, it was recommended that ILD progression should be evaluated by comprehensive assessments that include evaluations of respiratory muscle mass and function rather than FVC alone (101). Sarcopenia related respiratory muscle dysfunction may play a key role in the development of respiratory failure (61,103).

Summary of limb and respiratory muscle dysfunction

The relationship between sarcopenia and adverse events has been reported across several disease states (104-106). Sarcopenia is directly linked to physical inactivity but its impact on clinical outcomes has not well-described in ILD patients (107). Irrespective of the definition used across studies, sarcopenia appears prevalent with common risk factors including corticosteroid therapy, physical inactivity, increased bed rest from exacerbations, and hypoxemia. Sarcopenia can have important effects on overall well-being and functional capacity in ILD patients, which may bring out limitations in overall physical conditioning and cognitive function.

Cognitive limitations in ILD patients

The constraints of cognition limiting physical activities in ILD patients need to be considered because limb muscle movement is initiated and refined by cortical activation. Moreover, respiratory muscle function during elevated ventilation also requires cortical activation (108). Due to the demands of physical function on cortical activation, physical activities can be hampered by cognitive impairment. Even with normal cognitive capacity, movement could be further hindered by poor motor control and interference by other tasks that require cognition. This section will describe the limited evidence of cognitive impairment in ILD patients and how cognitive interference and poor motor control may further diminish physical activities in ILD patients.

Risk factors and prevalence

ILD patients have several risk factors (i.e., hypoxemia, inflammation, aging) associated with cognitive impairment, however, its prevalence is not well documented (109). A restrictive ventilatory pattern was correlated with worse cognitive performance in the Atherosclerosis Risk in Communities Study that examined a sample of 10,975 men and women (110,111). Smaller samples of patients showed evidence of decreased cognitive performance in those with severe IPF compared to those with more mild disease and healthier controls (112). Montreal Cognitive Assessment (MoCA) scores were lower in IPF patients compared to control subjects but not compared to COPD patients (109). Cognitive impairment was evident in more than one-third of sarcoidosis patients, regardless of disease severity (113) but was even more common in those with neurosarcoidosis, recruited from the Dutch Neurosarcoidosis Registry (114). While the prevalence is not well defined in ILD patients, neither are the underlying mechanisms, but several potential contributors have been suggested.

Potential contributing factors to cognitive impairment

Causes of cognitive impairments in ILD are likely multifactorial and may be similar to those described in COPD (115-117), however, no neurobiological model of underlying causes has been proposed. Several factors have been identified as potential contributors to cognitive interference or impairment including: disease severity, cardiopulmonary status, inflammation, obstructive sleep apnea (OSA), depression, dyspnea, and fatigue. Patients with more severe IPF demonstrated greater cognitive impairment (112). Inflammation has been acknowledged as a causative agent in sarcoidosis given the improvement in cognition and fatigue after anti-TNF-α therapy (113). Worse cardiopulmonary indices of 6MWD, post-exercise heart rate, and oxygen saturation before and after exercise were predictors of worse performance on cognitive tasks in 51 patients with ILD (118). IPF patients with more severe OSA had greater cognitive impairment (109). Although depression can influence cognition and was found in a small cohort of those with severe IPF, most participants scored below the clinical threshold for clinical intervention (112). Dyspnea showed a strong association with depression (119). Fatigue, reported to affect up to 95% of ILD patients, has been considered to be partly consequential to cognitive impairment (120) but the converse has not been described. Taken together, the interrelationships among disease severity, inflammation, cardiopulmonary status, OSA, depression, fatigue, and dyspnea as moderators or mediators of cognitive impairment in ILD patients require further investigation.

Does cognitive interference limit physical function?

The ability to assess the contribution of cognition on physical performance in clinical settings and research has been undertaken using dual-task paradigms. These paradigms challenge cognitive capacity because the simultaneous performance of two different tasks can call upon similar resources or exceed capacity. This can lead to errors or decreased performance of the given tasks, termed dual task or cognitive interference (121). Dual-task interference has been shown in older adults (122,123), neurological disorders (i.e., Parkinson's disease, stroke) (124-126), and COPD patients (121,122,127,128). Cognitive tasks used in the dual task paradigms applied in COPD patients included backwards spelling (121) and counting backwards (122,127,128). During dual tasking, decrements of the physical tasks were shown for gait speed (121,127), timed-up-and-go test (128), and balance (122). Given the evidence of dual-task interference in older adults and other disorders, the effect of cognitive interference on physical function will be important to explore in ILD patients.

Dyspnea's role in cognitive interference

Dyspnea, a predominant symptom in ILD responsible for diminished ADL, HRQL, and exercise capacity (24), may also play a major role in cognitive interference with physical function. Physical impairments in ILD have been primarily attributed to skeletal muscle dysfunction, disease severity, and dyspnea. However, it remains unclear whether dyspnea can impose more than just an unpleasant sensation on neurocognitive processing. Increased ventilatory demands activate cortical regions and are considered to be more conscious than quiet breathing (108). With a finite cortical capacity, greater sensations of dyspnea or increased cognitive demands could potentially interfere with cognition and purposeful movement in ILD patients, similar to what has been demonstrated in healthy people and COPD patients. Induced dyspnea by inspiratory threshold or resistive loading impaired facial recognition (129), reduced accuracy of a Stroop color word test (130), and decreased timed up-and-go performance (131) in healthy adults. Further, indoor walking showed decreasing prefrontal neural activity, a sign of automaticity, in older and younger adults but not in COPD patients (123,132). In a similar light, dyspnea may not only affect how ILD patients feel during physical exertion but may also limit or interfere with the available cognitive capacity required for well-controlled, coordinated movement during daily physical activities.

Cognition and activities of daily living

ILD appears to have a progressive, profound effect on ADL. Individuals with interstitial lung abnormalities are much less likely to be independent in activities of daily living [adjusted odds ratio 0.70 (0.55 to 0.90)] (133). The Glittre-ADL, a functional ADL test that evaluates trunk, arm, and leg movements showed worse scores in those with more severe ILD (134). Advanced IPF can even limit self-care such as showering and simple household chores (134,135). Dyspnea, mood, fatigue, and depression appear to be contributing and/or aggravating factors (134,135). Although limitations of ADL in ILD patients have not been explicitly attributed to cognitive interference or impairment, this requires further study.

Routine daily activities often require carrying out two or more tasks simultaneously, known as dual tasking or multi-

tasking (i.e., talking while walking or avoiding physical obstacles while walking). Automaticity can improve from single and dual-task training as shown in healthy adults and disorders such as stroke and amputees (136). There appears to be a transfer effect from cognitive training to physical tasks, such as with the timed-up-and-go test in older adults (136,137). Hand dexterity can also be improved through rehabilitation training, as shown in patients with neurological and rheumatoid conditions (138,139). Further, physical and cognitive training appears to induce distinct changes related to reaction time in dual-task performance (140). In fact, exercise training and physical activity (e.g., dance) can result in structural and functional changes in the hippocampus/parahippocampus area, the cerebellum, and the occipitotemporal cortex in adults older than 60 years (141,142).

Summary of cognitive limitations in ILD

Although cognitive impairment appears to be evident in ILD, the prevalence and the neurobiological model of underlying causes require further investigation. Regardless, the factors that contribute to cognitive interference during ADL (i.e., dyspnea) need to be defined. Lastly, many ADL require efficient coordinated movement such that exercise training during pulmonary rehabilitation could be advanced through a "motor control" lens that considers cognitive demands in addition to the current emphasis on aerobic and resistance training that primarily focus on peripheral muscle and cardiovascular adaptation.

Exercise training in pulmonary rehabilitation in ILD

Whole body exercise

Several studies provide evidence to support the benefits of pulmonary rehabilitation as a non-pharmacological therapy in ILD patients (76,143-146). It is an important therapeutic strategy because of its demonstrated, improved short-term outcomes for ILD patients irrespective of age, however, sustained benefits are less certain (147). Most studies report durations of 8 to 12 weeks but a couple of studies followed patients for 26 or 48 weeks (147). Recently, the effect of pulmonary rehabilitation in ILD has been comprehensively reported in an updated Cochrane Review (144). This review summarized evidence from 21 studies, of which data from sixteen studies were synthesized in meta-analyses (356 participants undertook pulmonary rehabilitation and 319 were control participants). Improvements in functional exercise capacity, dyspnea and HRQL were significant. In particular, the 6MWD was a sensitive outcome and exceeded its clinical minimum important difference with a mean improvement of 40 m (95% CI: 33–47) in 585 ILD participants. Holland *et al.* (56) emphasized that this updated Cochrane Review reported benefits of pulmonary rehabilitation that persisted as long as 6 to 12 months.

In general, the basic components of these programs are aerobic exercise training (i.e., walking, cycling) and resistance training (148-150). Systemic reviews have shown that pulmonary rehabilitation in ILD patients demonstrates significant improvements in exercise capacity, dyspnea and HRQL (144,149). Several previous reports have shown that exercise including resistance training actually improve sarcopenia in healthy older adults. Exercise programs have the potential to support muscle function in older people with sarcopenia (151,152). The evidence for peripheral muscle strength improvement in ILD has only been investigated in several studies, but there have been notable improvements in quadriceps strength with pulmonary rehabilitation (153,154).

Strategies for individual patient-tailored programs or reduction of exercise-induced hypoxemia and dyspnea are required to optimize training intensity. Because exercise-induced hypoxemia is common and may be severe in ILD patients, this issue needs to be addressed through the introduction of oxygen therapy and other strategies such as interval training to offset hypoxemia and recovery of oxygenation with rest. The intensity may need to be modified due to the inability of some ILD patients to perform the optimal prescribed load, especially in those who are frail or sarcopenic. One approach is to target an increase in total physical activity levels given that this is an important predictor of morbidity and mortality in patients with chronic respiratory diseases such as ILD (73,74,155).

As a countermeasure for ILD patients who exhibit significant desaturation, oxygen therapy during exercise is often used (156). The efficacy of supplemental oxygen in patients with IPF who have exercise-induced hypoxemia demonstrates that supplemental oxygen during exercise can improve endurance time, desaturation and subjective symptoms (157). Hence, the American Thoracic Society/European Respiratory Society (ATS/ERS) guideline statement regarding pulmonary rehabilitation recommends supplemental oxygen during exercise training for ILD patients (150,158).

Respiratory muscle training

Regardless of whether decrements in MIP are consistently

shown, work of breathing is increased in ILD due to decreased lung compliance and this is associated with dyspnea on exertion (159). Of interest, dyspnea has been associated with decreased MIP in some patients (160), suggesting a nonspecific association with ILD (161). Evidence that inspiratory muscle training (IMT) can improve dyspnea and mitigate functional aspects associated with ILD progression is limited by the paucity of well-designed studies. One randomized controlled double-blind study showed that 15 sarcoidosis patients, who received IMT for 6 weeks, improved functional and maximal exercise capacity, increased MIP, and improved fatigue and dyspnea (162). Notably, peripheral muscle strength did not improve (162). A systematic scoping review, albeit a small number of studies, cautiously reported the benefit of IMT on exercise capacity, dyspnea, and inspiratory muscle function in ILD patients (163). This scoping review was limited by the small number of available reports and by their designs. It included studies that examined IMT combined with pulmonary rehabilitation, IMT applied to both patients with obstructive and/or restrictive disease and case reports of IMT alone (59). Patients reported improved breathlessness, activities of daily living and mobility after IMT (164).

Given the well-established benefit of IMT on decreasing dyspnea sensation in other populations, IMT is worthy of further investigation in ILD patients.

Potential future directions in pulmonary rehabilitation

Pulmonary rehabilitation regimens have demonstrated that ILD patients improve skeletal muscle strength and endurance in response to training (144). Motor control, defined as the ability to perform purposeful movement, can be limited during physical activity and exercise even in those without discernable cognitive impairment. Although this is well described in healthy adults (165), there is limited recognition of this perspective in acute and chronic respiratory conditions (166-168). Future approaches to rehabilitation could explore the integration of motor learning, dual tasking, and improving automaticity as they pertain to physical ADL (136,169).

Training strategies, previously applied to other populations could potentially improve coordination, dual-tasking, and multifaceted physical ADL in ILD patients. Even in those without cognitive impairment, physical performance may be limited by motor control, which may be affected by factors that limit cognitive capacity such as dyspnea, affect, fatigue, sleep, pain, and motivation (109,120,170-172). Ongoing evaluation of the cognitive influence on physical activity may also be important to identify limitations that require simplification during physical activities (i.e., avoid or reduce cognitive demands during walking). Considering the benefit of exercise and physical activity in older adults, and the exacerbating influence of inactivity (173,174), motor control relevant to daily activities requires further study in ILD patients. Generally, pulmonary rehabilitation improves comorbid depression and anxiety in chronic respiratory patients (147). However, the effectiveness of pulmonary rehabilitation for dementia has not been explicitly investigated. Moreover, often times clinical manifestations associated with dementia are exclusion criteria (i.e., the ability to attend sessions on a regular basis). Although pulmonary rehabilitation has the potential to improve cognition or diminish cognitive interference, its impact on dementia remains unclear.

In addition, future refinement of exercise training for ILD patients should consider modifications of training parameters (i.e., frequency, intensity, type time) and choice of equipment. Interval training offers an alternative endurance training for ILD patients who may not be able perform the continuous prescribed load. A feasibility study of oxygen dependent ILD patients demonstrated that 20 min of interval exercise (30 s bouts at 100% of peak work) was preferred to continuous exercise (50% of peak work) and induced less end-exercise Borg fatigue and lower heart rate response (175). Interval training can provide the total training time by repetitive bouts rather than continuous exercise, while reducing dyspnea and fatigue (156). However, further research regarding interval training for ILD patients needs to establish the merit of this approach.

Clinical implications

The current review provides some clinical considerations in the ILD population given the increased age, comorbidities and polypharmacy experienced by this population (5-7). Irrespective of the frailty index utilized, the concept of frailty in ILD has been shown to be associated with increased risk of hospitalizations and elevated risk of readmissions. Given that ILD exacerbations and hospitalizations are a significant source of morbidity and mortality (28,30,32,34,54-57), identification of frailty parameters that are potentially modifiable such as weight loss, skeletal muscle dysfunction, and physical activity should be important considerations in the management of ILD patients (56,57). In addition, the concept of cognitive impairment and interference is gaining increased recognition in the COPD literature (176), with a

few studies now highlighting cognitive limitations in ILD. Thus, modifiable risk factors that can limit cognition, such as hypoxemia and dyspnea, need to be addressed by use of supplemental oxygen, increasing fitness, and utilization of energy conservation strategies. Consideration of a "motor control" lens in pulmonary rehabilitation that factors the contribution of dyspnea and motor learning on cognitive processing and multi-tasking, may prove to be a promising strategy in improving ADL and HRQL.

Conclusions

In recent years, treatments for ILD patients have improved with an evolving demographic of older patients and greater emphasis on frailty and physical function. Despite the high prevalence of frailty and skeletal muscle dysfunction in ILD, the underlying neurobiologic mechanisms require further definition. Cognitive impairment is evident in ILD, however, its implications for interference with physical daily activities is not well defined. The benefits of pulmonary rehabilitation's primary focus on strength and aerobic conditioning could be complemented by different strategies such as interval training and the integration of motor learning. This could potentially help improve transfer of rehabilitation strategies to physical daily activities and HRQL.

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Footnote

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Supplementary

Appendix 1 Detail of search strategy

Ovid MEDLINE(R) ALL <1946 to October 18, 2022>

#	Searches	Results	Type
1	exp Lung Diseases, Interstitial/	82,717	Advanced
2	Frailty/	7,578	Advanced
3	exp Muscular Atrophy/	20,188	Advanced
4	(Skeletal muscle* adj2 dysfunction*).mp.	958	Advanced
5	cognition disorders/ or exp cognitive dysfunction/	97,511	Advanced
6	sleep/ or sleep quality/	65,171	Advanced
7	exp Sleep Wake Disorders/	105,081	Advanced
8	exp Anxiety Disorders/	87,997	Advanced
9	exp Depressive Disorder/	119,380	Advanced
10	exp Anxiety/	106,079	Advanced
11	Depression/	144,504	Advanced
12	or/2-11	624,776	Advanced
13	1 and 12	362	Advanced
14	animals/ not (animals/ and humans/)	5,023,103	Advanced
15	13 not 14	360	Advanced
16	limit 15 to (English or Japanese)	307	Advanced

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CINAHL Ultimate (EBSCOhost)

#	Query	Limiters/expanders	Last Run Via	Results
S1	(MH "Lung Diseases, Interstitial+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	9,033
S2	(MH "Frailty Syndrome")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	3,782
S3	(MH "Muscular Atrophy+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	7,071
S4	TI Skeletal muscle* N2 dysfunction* OR AB Skeletal muscle* N2 dysfunction*	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	210
S5	(MH "Cognition Disorders+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	36,248
S6	(MH "Sleep Quality")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Ultimate	588
S7	(MH "Sleep Disorders+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	45,201
S8	(MH "Affective Symptoms+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	167,690
S9	(MH "Anxiety Disorders+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	51,498
S10	(MH "Depression+")	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	133,016
S11	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	289,267
S12	S1 AND S11	Expanders: Apply equivalent subjects Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	103
S13	S1 AND S11	Expanders: Apply equivalent subjects Narrow by Language: English Search modes: Boolean/Phrase	Interface: EBSCOhost Research Databases Search Screen: Advanced Search Database: CINAHL Ultimate	102

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