Clinical and Experimental Health Sciences

Respiratory Tract Diseases with Musculoskeletal System Interaction: A Scoping Review

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ABSTRACT

Objective: Respiratory diseases and musculoskeletal disorders are significant causes of morbidity and mortality worldwide, especially among older adults and immunocompromised individuals. Although current guidelines encourage a multidimensional approach to diagnosis and treatment, the interaction between these disease categories has not been adequately investigated. This scoping review aims to provide an overview of current research on diseases related to both respiratory and musculoskeletal disorders and identify gaps for future studies.

Method: Using the PRISMA extension to scope the reviews, we focused on randomized controlled trials and cohort studies published in the last five years. A total of 2003 abstracts were identified in databases such as Scopus, WoS, PubMed, Medline, Cinahl, OpenAIRE and EBSCO. After removing 287 duplicates, 1716 articles were screened based on title and abstract. A total of 470 full-text articles were assessed for eligibility, resulting in 11 articles meeting our inclusion criteria.

Results: The review shows limited but influential studies investigating the intersection between respiratory and musculoskeletal diseases. The findings suggest that musculoskeletal disorders may negatively affect respiratory functions and vice versa. Several studies have demonstrated potential biomarkers, the importance of sleep quality, and associations with multimorbidity.

Conclusion: Although limited to 11 articles, this review highlights the importance of a more detailed understanding of the interactions between the musculoskeletal system and respiratory diseases. This may inform future diagnostic and treatment strategies. However, the limited number of studies in this area indicates that more research is needed, especially which contains interaction mechanism of musculoskeletal and pulmonary pathologies.
Keywords: Musculoskeletal diseases, respiratory tract diseases, respiration disorders

1. INTRODUCTION

Respiratory infections are a major cause of death and illness around the world, and they are especially common and severe in older adults and people with weakened immune systems. Hospitalization ratio also higher in older adults who are affected with different types of respiratory infections (1). Musculoskeletal disorders also a become a worldwide problem in recent years, affects various comorbidities and other diseases such as psychological disorders (2). Its incidence is increasing in completely independent age and occupational groups in many parts of the world (2,3).

In a study which was conducted on 195 countries and areas showed that diseased that leads to or affected by musculoskeletal disorders needs to be diagnosed at early stages. Study also pointed that integrated strategies, prevention strategies and standardized clinical evidence-based treatment when dealing with musculoskeletal disorders (4).

In order to deal with respiratory diseases which has underlying effects of musculoskeletal disorders and comorbidities, clinicians/researchers have to use current guidelines that contains evidence-based and multidisciplinary perspective.

In the musculoskeletal system, controlling the airway opening and airway pressure and performing the coughing maneuver is only possible if the respiratory muscles work smoothly. Pathologies that may impair the function of the respiratory muscles or threaten their neurophysiological integrity may prevent the respiratory system from functioning. These pathologies may cause increased oxygen load, deterioration or change in the structure of the diaphragm, inability to manage the open-air pressure in the lower airways, and oxidative stress (5).

This integrity can lead holistic point of view in many diseases that has a relation pulmonary and musculoskeletal in both ways. Therefore, researchers who prepared this coping review be expectant that this study can enlighten the uncovered areas rapidly, lower the heterogeneity, and lead future studies to focus on this topic productively.

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2. METHODS

2.1. Review Protocol

The PRISMA extension for scoping reviews was applied on this review (6). Main and subheadings were created based on to cover this guideline's flow diagram.

2.2. Identifying the Research Question

Our research question was "What are the current approaches in diseases that related to both pulmonary and musculoskeletal disorders?" In this research, we conducted an analysis to highlight the gaps which are unfamiliar. We aimed to identify gaps in the research on combined musculoskeletal and pulmonary diseases in order to inform future studies on this topic.

2.3. Search Strategy and Selection Criteria

In this scoping review, we searched for only randomized controlled trials or cohort studies which were published in the last five years and conducted with only human participants. Search terms were "respiratory tract diseases" and "musculoskeletal diseases" and they were determined according to MeSH. We have used "and" for search operator. To avoid language barrier, studies written in English language were specified. Articles which were not met these criteria, were excluded.

2.4. Information Sources

Information sources were Scopus, WoS, Pubmed, Medline, Cinahl, OpenAIRE, EBSCO databases accessed via Marmara University VETIS Database Access and Statistics System.

2.5. Study Selection

Two researchers (RUE and TK) conducted a literature search in an electronic database. Researchers (RUE and TK) independently reviewed and screened the abstracts of the articles they found for inclusion.

2.6. Data Charting

A framework for standardized data extraction was developed. Relevant data were extracted independently by researchers (RUE and TK) and including process were applied after the number of the data sources were identified (Figure 1). After identification, extracted data were examined from both authors and articles which were relevant to inclusion criteria for both authors accepted as eligible. Extraction processes were contained reading full text of the article, using inclusion criteria and examining the relevance.

2.7. Data Analysis and Synthesis

Examination processes were contained four parts: 1. General information of studies 2. Study characteristics, 3. Design of the studies 4. Main and secondary findings.

2.8. Consultation Process

Data analyses were applied by researchers and a consultation request was made to a Prof. Tuğba Kuru Çolak, who has an expertise of musculoskeletal physiotherapy and rehabilitation, were examined analysis and synthesis process and assessed for bias, which has been not found.

3. RESULTS

In Figure 1, this study's designing process demonstrated and explained by using PRISMA-ScR. A total of 2003 abstracts identified at the beginning of study selection process. After removal of duplicates, 1246 articles excluded due to several considerations. The number of full-text accessible articles, 470 in number, were examined. 11 articles' data extracted and included into this study.

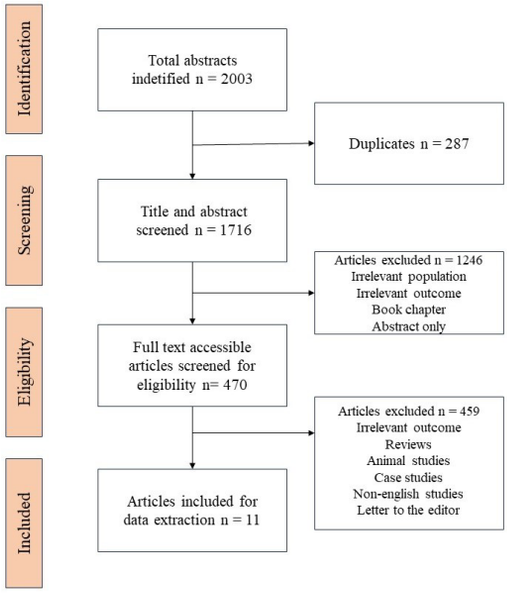

Figure 1. *Selection of Sources (PRISMA flow chart. PRISMA Extension for Scoping Reviews "PRISMA-ScR")*

Table 1 is a compilation of the characteristics and identifiers of the studies. According to Table 1, 8 of 11 studies indexed on Medline. There were 8 articles published in 2021, and there is one article published in each of the years 2018, 2020, and 2022. The studies included in our research consist of 5 different continents. While 5 studies included in our research were conducted in Europe and 3 studies in Asia; there is one study each from Africa, North America, and South America.

Table 2 consists of brief information of selected studies, which are detailed in terms of PRISMA-ScR topics. Our research focused on four different dimensions in each study: study design, outcome data, main results, and other analyses of these studies. Relevance of both respiratory and musculoskeletal disorders' information were highlighted in Table 2 to ensuring integrity of content.

Table 1. *Study Characteristics*

First Author, Ref.	Source of Index	Publisher	Year of Publication	Settings (Country, Continent)
Falksted D et al.[7]	Medline	Int Arch Occup Environ Health	2021	Sweden, Europe
Linden S et al.[8]	Medline	Eur J Cancer Care	2020	Sweden, Europe
Tazzeo C et al.[9]	EBSCO	Age Ageing	2021	Sweden, Europe
Ma KS et al.[10]	OpenAIRE	Eur J Orthod	2022	Taiwan, Asia
Elemary AMM et al.[11]	OpenAIRE	Egypt Rheumatol	2021	Egypt, Africa
Nakamura Y. et al[12]	Medline	Brain & development	2018	Japan, Asia
Katz P. et al.[13]	Medline	ACR Open Rheumatol	2021	USA, North America
Zhu X. et al.[14]	Medline	Front Mol Biosci.	2021	China, Asia
Botman E. et al.[15]	Medline	Bone Rep.	2021	Netherlands, Europe
Senel GB. et al.[16]	Medline	Sleep Breath.	2021	Türkiye, Europe
Paulin F. et al.[17]	Medline	Adv Rheumatol.	2021	Argentina, South America

Table 2. *Design of the Studies*

ID	Study Design	Outcome Data	Main results	Other Analyses
Falksted D et al.[7]	Prospective cohort study. 1,834,555 people between the ages of 44-63 were followed until they reached the age of 55-65. Physical workload, job control and job exposure measures were evaluated.	In participants diagnosed with cardiac and pulmonary disease, a statistically significant relationship was found between physical workload and disability pension status, but this was lower than average.	Swedish workers with higher physical workloads were more likely to receive disability pensions, according to the study	Relationship between disability pension and other status (education years, unemployment history, marital status, and job control) were evaluated in this study.
Linden S et al.[8]	This study examined the prevalence and incidence of comorbidities before non-small-cell lung cancer (NSCLC) diagnosis, as well as the impact of comorbidities on survival and mortality after diagnosis. A population-based cohort of NSCLC patients was identified and followed over time. The prevalence of comorbidities was measured at the time of diagnosis, and the incidence of new comorbidities was measured during follow-up. Median survival and mortality rates were also calculated.	Patients with cancer had more relevant comorbidities and higher incidence rates than the general population. In patients with NSCLC, mortality rates and incidence rates were highly correlated.	The study's findings can help caregivers better prepare to manage cancer patients, who are at increased risk for certain comorbidities and adverse outcomes. In the year leading up to their diagnosis, participants in this cohort were more likely to experience respiratory symptoms, infections, and cardiovascular diseases than the general population.	After diagnosis, patients with NSCLC were more likely to have anemia, central nervous system diseases, and respiratory diseases than comparators. Brain metastases and respiratory diseases were most likely due to the NSCLC itself.
Tazzeo C et al.[9]	Cross sectional and longitudinal cohort study. 2534 individuals were attended and 6-year (n= 2122) and 12-year (n= 2140) longitudinal assessment were applied. Relationship between multimorbidity patterns and frailty in elderly adults were investigated.	Statistically significance were found between physical frailty and mental, cardiovascular, metabolic and sleep disorders after 6 year.	Older adults with a combination of cardiovascular and neuropsychiatric diseases are most likely to become physically frail.	Multimorbidity in older adults is associated with lower quality of life, reduced functional independence, and increased mortality.
Ma KS et al.[10]	Population based 14-year cohort study. 2791 patients diagnosed with juvenile idiopathic arthritis were investigated in terms of obstructive sleep apnea risk. Control group consisted of 11164 matched participants without juvenile idiopathic arthritis.	95 participants diagnosed with obstructive sleep apnea (OSA) and ratio of diagnosed patients were more on juvenile idiopathic arthritis (JIA) group, statistically significance was found. OSA risk was increased after 5 year of JIA diagnosis.	This study found that patients with JIA have a higher risk of OSA and a higher prevalence of OSA. Sleep quality was low in JIA patients, and sleep dysfunction symptoms were common.	This study also explored possible mechanisms causing the increased risk of OSA in JIA patients and evaluated the effects of OSA on treatment strategies and clinical management in JIA patients.

Elemary AMM et al.[11]	Retrospective study based on 100 rheumatoid arthritis patients with pulmonary disorders. It was aimed that to determine the relation between rheumatoid arthritis, and pulmonary involvement type and its frequency.	High resolution computed tomography showed that 68% of patients had abnormalities, and the ground glass were most common (52.9%).	Chest tomography with high resolution was found to be a more sensitive diagnostic tool for pulmonary abnormalities than spirometry in patients with rheumatoid arthritis. Passive smoking, chronic cough, a high Larsen score, and high levels of anti-cyclic citrullinated peptide antibodies were all significant predictors of lung involvement as detected by high-resolution computed tomography.	A significant association was found between pulmonary function tests and high-resolution chest tomography findings. Additionally, age was found to be significantly associated with high-resolution chest tomography-diagnosed pulmonary abnormalities.
Nakamura Y. et al[12]	This study retrospectively evaluated six young adults with Becker muscular dystrophy (BMD) to assess sleep hypoventilation. The goal was to develop predictive estimates of non-invasive ventilation (NIV) initiation in BMD patients by monitoring nocturnal forced vital capacity (FVC), forced expiratory volume in one second (FEV1%), peak expiratory flow (PEF%), peak cough flow (PCF), and average PCO2. Additionally, the researchers investigated the significance of sleep hypercapnia.	Patients with BMD often experience isolated sleep hypercapnia in the early stages, despite preserved waking lung function. However, the significance of respiratory failure in BMD and the ideal timing of NIV warrant further investigation.	Five patients with BMD, three of whom were mobile, experienced elevated PCO2 levels above 45 mmHg during sleep. NIV was initiated in four patients. While one BMD patient with an exon 3-7 deletion had gradual declines in FVC% and PEF, these functions remained stable in other BMD patients. Sleep hypercapnia, which is unexpected based on routine pulmonary function tests, has been observed in patients with BMD.	The average carbon dioxide levels (PCO2) of BMD patients during sleep were lower than the levels measured with the CO2 (end-tidal carbon dioxide, EtCO2) monitor from the esophagus. However, this was consistent with the observation of sleep hypercapnia at younger than expected ages reported in previous studies. Five patients in this study experienced peak PCO2 levels of 52-54 mmHg overnight. Other analyses, such as the causes of sleep hypoventilation, treatment options, and the impact of this condition on the prognosis of muscular dystrophy, are also included in the article.
Katz P. et al.[13]	This article was conducted to investigate the prevalence of asthma and COPD (Chronic Obstructive Pulmonary Disease) in systemic lupus erythematosus (SLE) patients and their effects on the patients' health-related quality of life. Two different patient groups (FORWARD "n=2804" and LOS "n=881") were included in the study.	The findings of this study showed that the prevalence of asthma and COPD is higher in SLE patients than in the general population. In addition, the presence of these diseases has been found to adversely affect patients' physical functioning, fatigue, perceived cognitive function, and pain. These findings suggest that SLE patients should be screened regularly for asthma and COPD and ensure they receive adequate treatment for these conditions.	In the initial observations, 19.8% of the FORWARD group (FORWARD participants were selected primarily from rheumatologists' patients and diagnosed with SLE by a rheumatologist) reported asthma and 8.3% COPD. The LOS (Lupus Outcome Study was a longitudinal observation cohort in which participants completed annual structured telephone interviews. All SLE diagnoses were physician-confirmed), whereas 36% of participants reported either asthma or COPD.	In the FORWARD group, the mean age was 50.5 (±14.1) years, the white non – Hispanic rate was 87.2%, the mean duration of SLE was 15.8 (±12.3) years, the low education rate was 6.3%, and the obesity rate was 36.1%. In the LOS group, the mean age was 46.7 (±12.7), the rate of being white was 68.5%, the mean duration of SLE was 12.6% (±8.5) years, the rate of low education was 19.6%, and the obesity rate was 25.7%.
Zhu X. et al.[14]	This article compares the salivary gland gene expression profiles of patients with (n=36) and without (n=128) primary Sjögren's syndrome (pSS) with interstitial lung disease (ILD).	The article examines the relationship between interstitial lung disease and CXCR2 levels in patients with primary Sjögren's syndrome and the potential of CXCR2 in predicting disease activity. The findings of the article suggest that CXCR2 may be a potential biomarker for monitoring and evaluating the course of the disease in ILD-pSS patients.	As a result of analyzes performed on 36 ILD-pSS patients and 128 non-ILD-pSS patients in total, some genes expressed at high levels in ILD-pSS were identified. The researchers noted that among these genes, CXCR2 in particular could be a potential biomarker to assess the severity of the disease. CXCR2 levels were found to be abnormally increased in ILD-pSS patients and these elevated levels were associated with clinical features.	Other analyzes such as the role of CXCR2, its relationship with other inflammatory markers, its prognostic value and its effects on response to treatment are also included in the article. It was determined that CXCR2 was highly correlated with Erythrocyte Sedimentation Rate (ESR) and ESSDAI scores, which are other parameters that play a role in assessing the course of the disease, and inversely correlated with DLCO.

Botman E. et al.[15]	This study was conducted to evaluate how lung function changes over time in patients with Fibrodysplasia Ossificans Progressiva (FOP) (n=7) and its relationship with the volume and progression of heterotopic ossification (HO) in the lung.	The research shows that respiratory function is impaired at an early age in FOP patients and this deterioration stabilizes over time, and this deterioration is mostly due to small lung volumes and jaw ankylosis.	A decrease in FVC was observed in three patients. The decline was seen during childhood and early adolescence. TLC decreased in 2 patients. In one patient, the discrepancy between FVC and TLC was caused by an increase in the RV/TLC ratio. This rate was higher than expected in all patients. Additionally, FEV1 was observed to decrease over time in 3 patients. In one patient, mouth opening increased to a few millimeters after surgery, resulting in an increase in FEV1. TLC, FVC and RV/TLC ratio did not change due to increased mouth opening.	The patients' FEV1 values were decreased, but the Tiffeneau index was within normal limits. The decreased FEV1 value may be due to decreased lung volumes in FOP patients. Also, jaw ankyloses can affect FEV1 values. FVC and VC values decreased, indicating restrictive respiratory function. TLC values were found to be normal in only one patient. Increased residual volume (RV) was observed in most patients, representing the difference between TLC and VC. In FOP patients with complete ankylosis of the thorax, RV increased, and TLC decreased. In addition, mild abnormalities were seen in the pulmonary parenchyma. In addition, the vertebral integrity of the patients was evaluated, and their kyphosis and scoliosis status were examined.
Senel GB. et al.[16]	The aim of this study is to investigate the effect of obstructive sleep apnea syndrome (OSAS) on cardiac autonomic dysfunction in Duchenne muscular dystrophy (DMD) patients (n=12) (Total N=20).	The study showed that 42% of DMD patients had OSAS and cardiac autonomic dysfunction was more pronounced in these patients. It was also found that heart rate variability (HRV) parameters are abnormal in DMD patients and OSAS plays a role in cardiac autonomic dysfunction as demonstrated through HRV parameters.	Twelve male DMD patients (mean age 9.0 ± 3.1 years, mean BMI 20.6 ± 4.8 kg/m2) and eight healthy men of the same age were included in the study. At clinical evaluation, 58% of patients with DMD had at least one OSAS-related symptom (snoring, observed apnea, or restless sleep). None of the individuals in the control group had any OSAS-related complaints. According to PSG, OSAS was detected in 42% of patients with DMD, while OSAS was not detected in any individual in the control group (p=.004). The mean R-R duration and the mean of consecutive R-R intervals longer than 50% ms were significantly lower in DMD patients than in the control group (p<.006). In DMD patients with OSAS, the LF/HF (low/high frequency) ratio during NREM sleep was significantly higher than in the control group (p=0.005). Higher apnea-hypopnea index and lower oxygen saturation were significantly correlated with higher LF power and LF/HF ratio (p<.001).	In the article, total sleep time, sleep latency, REM sleep latency, sleep efficiency, peak PaCO2 values, periodic leg movements index values, N1, N2, N3 and REM sleep times were determined as additional parameters evaluated.
Paulin F. et al.[17]	This multicenter cross-sectional study investigated the prevalence of pulmonary involvement in patients with early rheumatoid arthritis (RA) without pre-existing lung disease. In the study, 83 early RA patients were included, and lung involvement was evaluated with high-resolution computed tomography (HRCT).	The findings showed that patients with early RA have a high rate of lung involvement affecting the airway and that all types of lung involvement are associated with abnormalities in physical examination findings and functional tests.	83 patients (83% female) were included in the study. The median time elapsed after the diagnosis of RA was 3 (1-6 months). HRCT revealed airway involvement in 57 patients (72%) and interstitial abnormalities in 6 patients (7.5%). The most common change in lung function tests was decreased DLCO (14%). Patients with at least one abnormality on physical examination were found to be associated with lung involvement on HRCT. In addition, FVC% and DLCO% values were significantly lower and RV/TLC values were higher in patients with lung involvement. It was found that any variable associated with joint involvement was not associated with abnormalities in HRCT.	In addition to the parameters evaluated in the study, patients' comorbidities, dyspnea duration, physical abnormality assessments, articular and extra-articular parameters, inflammatory parameters and the presence of anti-Ro antibodies were investigated. The presence of anti-Ro antibody has been associated with interstitial abnormalities in HRCT.

4. DISCUSSION

The interaction between musculoskeletal problems and respiratory tract diseases has been addressed in a limited number of studies. However, examining this interaction is especially important because of its potential effects on an individual's quality of life and overall health. The subject of this research was determined to examine this interaction.

Falksted et al. (7) showed that high physical workload among middle-aged and older workers increases the likelihood of receiving a disability pension. This finding indirectly reveals the potential impact of musculoskeletal problems on the respiratory system. It is conceivable that disability-related retirement may be an indicator of a significant decline in a person's functionality and general health.

At the same time, a study conducted by Linden et al. (8) showed that cancer patients have higher rates of comorbidity than the general population. These comorbidities include respiratory symptoms, infectious diseases, and cardiovascular diseases. This may be further evidence of the impact of musculoskeletal problems on the respiratory system.

Tazzeo et al. (9) revealed that the burden of multimorbidity in older adults has negative effects on quality of life, functional independence and mortality. This study shows that musculoskeletal problems, and especially cardiovascular and neuropsychiatric diseases related to these problems, can have a significant impact on the general health status of individuals.

Studies conducted by Ma et al. (10) and Elemary et al. (11) have shown that certain musculoskeletal diseases (juvenile idiopathic arthritis and rheumatoid arthritis, respectively) can lead to respiratory disorders. These studies show that musculoskeletal diseases can have a direct impact on the occurrence and development of respiratory system diseases.

Katz et al. (13) showed that the prevalence of asthma and COPD was higher in Systemic Lupus Erythematosus (SLE) patients than in the general population. This suggests that SLE, an autoimmune musculoskeletal disease, can have a potentially serious impact on the respiratory system.

The study by Nakamura et al. (12) examined sleep hypoventilation in patients with Becker muscular dystrophy (BMD) and its effects on respiratory functions. The results of the study showed that lung functions were preserved during waking hours, but hypercapnia developed during sleep in BMD patients. It has been mentioned that isolated sleep hypercapnia may develop especially in the early stages of BMD patients. However, it was stated that the optimal timing of respiratory failure and non-invasive ventilation (NIV) should be investigated further.

In another study by Zhu et al., (14) they compared the gene expression profiles of patients with primary Sjögren's syndrome (pSS) and patients with pSS (ILD-pSS) diagnosed with interstitial lung disease (ILD). The findings of this study suggest that CXCR2 may be a potential biomarker to monitor and evaluate the course of the disease in ILD-pSS patients.

The study conducted by Botman et al. (15) focused on how lung function changes in patients with Fibrodysplasia Ossificans Progressiva (FOP) and how this change relates to heterotopic ossification (HO). The findings showed that respiratory functions were impaired at an early age in FOP patients, and this deterioration was mostly due to low lung volumes and jaw ankylosis.

Research conducted by Senel et al. (16) examined the effects of obstructive sleep apnea syndrome (OSAS) on cardiac autonomic dysfunction in patients with Duchenne muscular dystrophy (DMD). The study showed that 42% of DMD patients had OSAS and cardiac autonomic dysfunction was more pronounced in these patients.

The study conducted by Paulin et al. (17) examined the prevalence of pulmonary involvement in patients with early rheumatoid arthritis (RA) without pre-existing pulmonary disease. The findings showed that patients with early RA have a high rate of lung involvement affecting the airway and that all types of lung involvement are associated with abnormalities in physical examination findings and functional tests.

5. CONCLUSIONS

These studies help us better understand the effects of various diseases on the respiratory system and general body functions. The findings show us that the impact of musculoskeletal problems on the respiratory system is important and requires further investigation of this interaction. Such research can provide a more effective approach to respiratory tract diseases of individuals with musculoskeletal problems and help develop strategies to manage these conditions. In addition, research in the literature review contributes to the understanding of various biomarkers and markers that are important in the diagnosis and management of diseases. Especially respiratory functions, sleep quality and gene expression profiles seem to play an important role in the course and treatment of musculoskeletal diseases. However, an important conclusion identified in the studies is that the nature and mechanism of the interaction of musculoskeletal diseases with respiratory tract diseases is still not fully understood and more research is needed on this subject.

Our research covers the studies conducted in the last five years. For this reason, there was a limitation of the studies related to the aim of the research since the previous studies were not looked at.

In the screening conducted for the purpose of our research, it was determined that there were no studies that directly evaluated the "effects of musculoskeletal problems on the respiratory tract and respiratory system". This situation emerged as one of the limitations of the research.

The lack of randomized controlled studies and their inability to use them in this study, due to the limited resources obtained as a result of the search of databases, is another limitation.

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