ORIGINAL ARTICLE

A Meta-analysis on the Effectiveness of Exercise in Improving Lung Function in Children with Post-operative Congenital Diaphragmatic Hernia

Kevin L. Bautista, MD* and Angelica Niña F. Datingaling, MD*

Division of Pediatric Pulmonology, Department of Pediatrics, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Background and Objective. Pediatric post-operative congenital diaphragmatic hernia (CDH) patients have been shown to encounter reduced pulmonary function tests (PFT) potentially leading to respiratory symptoms. Strategies involving exercise have been used to improve PFT. This meta-analysis aims to determine the effectiveness of exercise in improving lung function in pediatric post-operative CDH patients.

Methods. An electronic search was done on May 2023 in MEDLINE via Pubmed, Cochrane Library, Embase, ClinicalKey, Scopus, Google Scholar, and Herdin Plus, using the search terms "exercise" and "congenital diaphragmatic hernia" and "children" or "pediatric" and "pulmonary function" or "lung function". The study included pediatric patients in whom CDH has been surgically corrected, and excluded patients who were unable to perform the test maneuvers, have cardiopulmonary instability, and have serious associated anomalies. Randomized controlled trials (RCT) were identified and independently assessed by two review authors. Each RCT was independently assessed for bias by two review authors using the Cochrane Handbook for Systematic Reviews of Interventions. The RevMan 5.4 software was used for statistical analysis.

Results. A total of 124 participants from three studies were included in the meta-analysis. The pooled mean difference showed a significantly higher mean functional vital capacity (FVC) (MD=6.12, 95%CI=3.91 to 8.33, *p*-value<0.00001) and forced expiratory volume in 1 second (FEV_1) (MD=6.25, 95%CI=3.39 to 9.10, *p*-value<0.0001) in the study group compared to the control group.

Conclusion. Exercise may be effective in improving lung function in children with pediatric post-operative CDH. However, the study is limited by its small sample size, the lack of assessment of long-term outcomes, and the difference in exercise regimens used in each RCT. Further studies are recommended to determine the most optimal exercise regimen and to measure its effect on the other outcomes for this population.

Keywords: Exercise, congenital diaphragmatic hernia, children, pediatric, pulmonary function, lung function

** Dr. Bautista and Dr. Datingaling shared first authorship for this manuscript.*

Paper presentation – Fellow's Research Forum: Systematic Review Category, October 17, 2023, Philippine General Hospital, University of the Philippines Manila.

Corresponding author: Angelica Niña F. Datingaling, MD
Division of Pediatric Pulmonology
Department of Pediatrics
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: anfd92@gmail.com

INTRODUCTION

Congenital diaphragmatic hernia, a structural defect of the diaphragm causing communication between the chest and the abdomen that leads to herniation of the abdominal contents into the thorax, occurs in an estimated 1 in 2000 children.[1] In the Philippines, a search in the Childhood Disease Registry of the Philippine Pediatric Society yielded a result of 790 cases of congenital diaphragmatic hernia.[2]

Neonates with CDH usually present with significant respiratory distress at birth. Furthermore, since CDH occurs in the pseudoglandular phase of lung development at 6 to 17 weeks post conception, it is often associated with other congenital lung diseases, particularly pulmonary hypoplasia, the leading cause of death in these children. Approximately 50% of these children also have non-pulmonary complications such as cardiovascular lesions, omphalocele, and neural tube defects.[3,4]

Prognosis for children with CDH was generally poor, but advances in management approach and surgical repair have been made to improve survival rates to 70 to 92 percent.[4] Despite this, studies have shown that post-operative CDH patients have evidence of respiratory limitations and lower exercise capacity due to decreased pulmonary function, which continues to decline with age.[5,6] Hence, strategies involving respiratory muscle training and exercises to improve exercise capacity, lung function, and overall quality of life in post-operative CDH patients have been investigated.[7,8]

Significance of the Study

Respiratory disease in post-operative CDH patients, sometimes referred to as CDH survivors, involves identified and hypothesized abnormalities such as lower total lung volumes due to impaired lung development and diaphragmatic function, decreased lung compliance, and decreased respiratory muscle strength, more evident in those who were on mechanical ventilation in the neonatal period.[7,9,10] Lung volume studies have shown both obstructive and restrictive patterns in these patients.[11] Reported symptoms of respiratory disease in CDH survivors include exertional and nocturnal dyspnea, dyspnea at rest, chest pain, and recurrent respiratory infection.[5] Other long-term consequences found in these patients are bronchopulmonary dysplasia, pulmonary hypertension, poor nutritional status, gastroesophageal reflux disease, and neurological and developmental disabilities.[12]

These comorbidities pose both a significant health burden and an economic burden to the patients and their caretakers. This led to studies regarding health-related quality of life in this population, with a recent study showing that quality of life scores were lower in CDH survivors and their families compared to controls, with readmissions due to respiratory disease identified as the leading cause of burden.[5,13] These issues emphasize the importance of a multi-disciplinary approach and monitoring on long-term follow-up.

Pulmonary rehabilitation has been shown to be a valuable non-pharmacologic intervention in patients with chronic respiratory disease, aiming to improve health, functionality, and quality of life of these patients through therapies such as aerobic exercise training, breathing exercises, educational programs, and behavioral modifications, usually in the outpatient setting. In particular, it can improve exercise tolerance and decrease perception of dyspnea.[14] These benefits were demonstrated in patients with obstructive diseases such as chronic obstructive pulmonary disease and asthma, and less commonly in patients with restrictive diseases such as interstitial lung disease.[14-17] Recent studies have demonstrated that CDH survivors with athletic lifestyles had higher exercise capacity than those who were sedentary,[5,18] but the question of whether timely interventions can improve the outcomes of these patients remains.

Long-term respiratory complications associated with post-operative CDH may be decreased by applying interventions that improve lung function. The strength of evidence of studies involving these interventions should be investigated so that recommendations for their application in clinical practice can be established.

Review of Related Literature

Pulmonary function and exercise capacity in CDH survivors

Pulmonary function tests (PFTs) are important tools in determining respiratory disease status and its progression, with special importance in children who are in a crucial phase of lung development and growth. It provides an insight in gauging the lung resistance and compliance, aiding in decision-making. The most commonly used tool in cooperative children and most readily available in the local setting is spirometry, which mainly measures the following outcomes: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), ratio of FEV_1 and FVC (FEV_1/FVC), and forced expired flow between 25% and 75% of expired FVC (FEF_{25-75}).[1] Typically, a result showing reduced FEV_1 and FEV_1/FVC is consistent with an obstructive pathology, while reduced FEV_1, reduced FVC, and normal FEV_1/FVC implies a restrictive pathology. Decreased FEF_{25-75} indicates small airway obstruction. Some disease entities may present with both obstructive and restrictive pathology.

Several studies have been undertaken measuring the pulmonary function of CDH survivors for long-term care and monitoring, as it is postulated that most of these patients will have respiratory morbidities as they grow older. Infant PFTs have demonstrated obstructive airway disease, related to the degree of pulmonary hypertension and pulmonary hypoplasia in the neonatal period. In a study by Dao et al. in which pulmonary function monitoring with spirometry was done multiple times for 74 CDH survivors from 5 to 27 years of age, results showed a progressive decline in FEV_1 and FEV_1/FVC with age, implying a progressing obstructive airway disease.[6]

Peetsold et al. performed spirometry in 53 CDH survivors which showed reduced FEV_1, FVC, and FEV_1/FVC among almost 50% of the sample size. The obstructive pattern of disease was attributed to impaired lung development leading to a distorted lung architecture, and to barotrauma from mechanical ventilation in the neonatal period. Low total lung capacity was demonstrated in a number of patients, but was not found to be statistically significant. Interestingly, the author did a similar study among adult CDH survivors which also showed restrictive airway disease in 25% of the sample size, but further studies were recommended.[11]

In a systematic review by Lewis et al., pulmonary function test results were compared across different studies, although limited by heterogeneity among the studies. Review of the studies showed a consistent reduction in FEV_1, FVC, and FEV_1/FVC among pediatric CDH survivors versus controls. Factors that were associated with reduced PFTs include diaphragmatic defect size, duration of mechanical ventilation at birth, and lower body mass index. Another study showed significant air trapping on body plethysmography in a subset of patients. Additional findings in this review are reduced health-related quality of life and reduced exercise capacity.[19]

While some previous studies showed that CDH survivors have a normal exercise capacity and show no physical impairment,[11] more recent studies show otherwise. In the study of Bojanic et al., cardiopulmonary exercise testing was done on 22 CDH survivors. Variables measured at peak exercise were breathing pattern, maximal oxygen consumption (V_{O2}), minute ventilation (V_E), carbon dioxide production (V_{CO2}), and oxygen pulse (O_2 pulse), which reflects the amount of oxygen used by the exercising muscle. Findings revealed that the CDH survivors had an aerobic peak power below expected for age, limited in their ability to increase their O_2 pulse and tidal volume. Among the CDH survivors, higher maximum exercise capacity was observed in those with athletic lifestyle as opposed to those who were sedentary.[5] Similar findings of decreased exercise capacity in CDH survivors were demonstrated in studies by Miles et al. and Toussaint-Duyster et al.[20,21]

Exercise and respiratory muscle training

Ventilation is a multifactorial process, an interplay between central controller in the brain, sensors such as chemoreceptors, and effectors or the respiratory muscles. Dysfunction in any component will lead to suboptimal respiration and ventilation. Muscles of inspiration are the external intercostal muscles, accessory muscles of inspiration consisting of scalene and sternomastoids, and diaphragm, the most important muscle of inspiration. On the other hand, expiration is a passive process, but exercise and hyperventilation activate the muscles of active expiration which are the abdominal wall muscles and internal intercostal muscles.[22]

Obstructive lung disease leads to increased demand on the inspiratory muscles due to dynamic hyperinflation. Expiratory flow limitation leads to air trapping and an imbalance of the lung forces, leading to need to initiate inspiration with a positive expiratory load. This also places the inspiratory muscles at a functionally weaker position of force and causes shortened inspiratory time to allow longer expiration. Furthermore, obstructive diseases lead to decreased tidal volume and increased dead space. These processes lead to ventilation-perfusion mismatch, inefficient breathing patterns, muscular deconditioning, and eventually respiratory fatigue, manifesting as difficulty of breathing, reduced exercise capacity, and decreased quality of life.[23]

Previously, studies done on effects of respiratory muscle training on obstructive disease showed unconvincing evidence of its benefit, but recent studies, specifically on asthma and chronic obstructive pulmonary disease, showed its positive effect on inspiratory muscle strength, exercise capacity, and decrease in dyspnea during exertion and in daily activities.[23] In a meta-analysis by Wang et al., it was found that inspiratory muscle training enhanced pulmonary function and increased FEV_1 in patients with stable asthma.[24] Likewise, a meta-analysis conducted by Figueiredo et al. showed an improvement in inspiratory muscle strength, measured by maximum inspiratory pressure (MIP), and FEV_1 after six to eight weeks of training.[25] Crisafulli et al. found improvement in dyspnea at rest and at exercise in a randomized controlled trial among patients with COPD who underwent respiratory muscle training. On the other hand, expiratory muscle training is still to be further investigated in patients with COPD.[26] McConnell recommends that inspiratory muscle training be done at a minimum of once a day, increasing the load weekly, for at least six weeks. After this period, frequency can be reassessed and reduced.[23]

In a study by Turchetta et al., it was noted that in a group of 18 pediatric CDH survivors, those with regular programmed physical activity had improved exercise capacity and perception of dyspnea than those without, leading to the conclusion that exercise and training may improve ventilation in these patients.[18] Bojanic et al, had similar findings that, although CDH survivors had increased incidence of pulmonary disease and decreased exercise capacity compared to normal children, among the cohort of CDH survivors, those with a physically active and athletic lifestyle had higher exercise capacity and FEV_1 and FVC than those who were sedentary.[5]

OBJECTIVES

General Objective

This study aims to determine the effectiveness of exercise in improving lung function in pediatric post-operative congenital diaphragmatic hernia patients.

Specific Objectives

1. To determine the effect of exercise in improving FEV_1, FVC, and FEV_1/FVC in pediatric post-operative CDH patients

2. To determine the effect of exercise in increasing exercise capacity in pediatric post-operative CDH patients
3. To determine the effect of exercise in improving quality of life (QOL) in pediatric post-operative CDH patients

METHODS

Search Criteria

Types of studies

This study included available published randomized controlled trials (RCTs) in any language, testing whether exercise could improve lung function in pediatric post-operative CDH patients.

Types of participants

The participants included in this study were pediatric patients in whom CDH has been surgically corrected. This study excluded patients who were unable to perform the test maneuvers, have cardiopulmonary instability, and have serious associated anomalies.

Types of intervention

The RCTs included in this study involved any type of exercise in CDH survivors in an outpatient setting. Comparisons were made between exercise versus standard incentive spirometry training or physical therapy.

Types of outcomes

Primary outcomes

The primary outcome is the improvement in lung function tests (FEV_1, FVC, and FEV_1/FVC) achieved by the CDH survivor.

Secondary outcomes

The secondary outcomes are the following:

a. Maximal oxygen intake, minute ventilation, and carbon dioxide production at peak exercise
b. Score in a pediatric quality of life questionnaire

Search Methods

Electronic searches

An electronic search was done in MEDLINE via Pubmed, Cochrane Library, Embase, ClinicalKey, Scopus, Google Scholar, and Herdin Plus, using the search terms "exercise" and "congenital diaphragmatic hernia" and "children" or "pediatric" and "pulmonary function" or "lung function". The search was done on May 2023 and was limited to RCTs and clinical trials with publication date within the last five years, without any language restriction. The electronic search study flow diagram is shown in Figure 1. Reasons for exclusion of articles are their irrelevance to the subject, having a different intervention, or having a different disease entity being investigated.

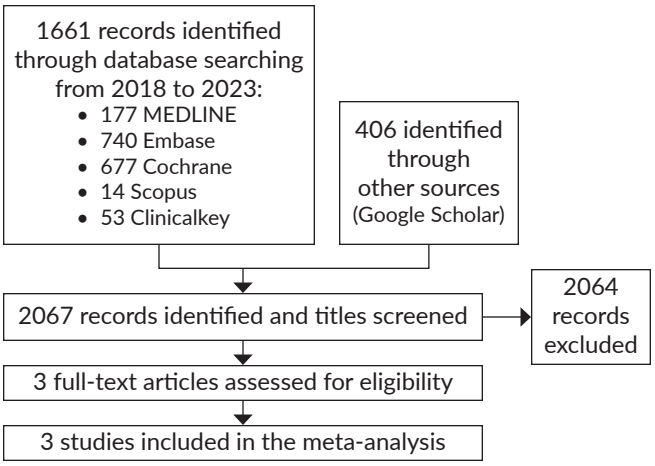

Figure 1. Electronic search study flow diagram with use of the keywords "exercise" and "congenital diaphragmatic hernia" and "children" or "pediatric" and "pulmonary function" or "lung function".

Searching other resources

Direct correspondence with authors and experts, and review of related articles were done.

Data Collection and Analysis

Selection of studies

The eligibility of full text articles of RCTs was independently assessed by two review authors. This review included three identified RCTs.

Data extraction and management

Data from each RCT were extracted by two review authors who worked independently to avoid mistakes and bias. Details that were included in the meta-analysis are study title, authors, year published, study duration, study design, participants, randomization, interventions, outcomes, and outcome measures. The authors resolved disagreements with proper discourse, consulting a third party if an agreement was not reached. The Review Manager Version 5.3 (RevMan) software was used to analyze the data obtained.

Assessment of risk of bias in included studies

Each RCT was independently assessed for bias by two review authors using the Cochrane Handbook for Systematic Reviews of Interventions.

a. Sequence generation
   Allocation sequence generation methods were evaluated for selection bias. these methods were categorized as:
   - low risk – any truly random process, such as drawing lots, random table of numbers, or random number generated by a computer

- high risk – any non-random process, such as patient case number, or odd or even date of birth
- unclear risk – incomplete data

b. Allocation concealment
Allocation sequence concealment methods were assessed for selection bias. These methods were categorized as:
- Low risk – such as adequately sealed, consecutively numbered, opaque envelopes, telephone or central randomization
- High risk – such as non-opaque or inadequately sealed envelopes, alteration, open random allocation
- Unclear risk – incomplete data

c. Blinding
Blinding of the personnel and outcome assessors was assessed for performance bias. The methods used were categorized as:
- Low risk, high risk, or unclear risk for personnel
- Low risk, high risk, or unclear risk for outcome assessors

d. Incomplete outcome data
Each study was evaluated for completeness of data, reporting of attritions and exclusions, comparing numbers in each stage of analysis with the total count of participants, and whether missing data were equalized across groups or were related to outcomes. To assess for attrition bias, missing data were assessed as:
- Low risk - no missing data, or reasons for missing data were stated and balanced across groups
- High risk - missing data affected outcomes or not balanced across groups
- Unclear risk – insufficient data

e. Selective reporting bias
Selective outcome bias was evaluated as:
- Low risk – pre-specified and all expected outcomes of the study were reported
- High risk – pre-specified and expected outcomes, or results of a key outcome were incompletely reported
- Unclear risk – insufficient data

f. Other sources of bias
Other possible sources of bias were investigated and assessed as:
- Low risk – without other possible sources of bias
- High risk – with risk of bias
- Unclear risk – insufficient data

Measure of treatment effect

Continuous outcomes will be reported as mean differences between treatment and control. The RevMan 5.4 software was used in analyzing results.

Assessment of heterogeneity

Cochran's Q test and I^2 index were used in the assessment of heterogeneity across studies. The null hypothesis, if the studies were homogeneous, was rejected if the p value of the test was below 0.10, or I^2 was more than 50%. Meta-regression to explore sources of heterogeneity was not performed given the small number of studies included in the meta-analysis.

Data synthesis

The RevMan 5.4 software was used for statistical analysis.

Sensitivity analysis

Sensitivity analysis was done to evaluate the effect of the individual studies on the pooled result for FVC and FEV_1. This was not done on other outcomes since only two studies were included on the other forest plots.

Subgroup analysis

Subgroup analysis by age groups and study quality were initially intended. However, given the small number of studies included in the meta-analysis, this was not feasible.

Certainty assessment

The GRADE approach was used for assessing the certainty of evidence. The highest quality rating is for randomized trial evidence. The authors downgrade randomized trial evidence to moderate, low, or even very low quality evidence, depending on five factors: limitations in study design, indirectness, unexplained heterogeneity, imprecision of results, and risk of publication bias.

Ethical Considerations

There were no identified ethical issues in the study design, ethics approval, data analysis, authorship, redundant publication, and plagiarism in this study. There were no conflicts of interest among the authors. The manuscript was submitted to the University of the Philippines Manila Research Ethics Board for review and was confirmed to be similar to studies that are typically exempt from ethical review based on the National Ethics Guidelines for Research Involving Human Participants 2022. This study is registered at the University of the Philippines Manila Research Grants Administration Office with the registration number RGAO-2023-0890.

RESULTS

Three studies, all based in Saudi Arabia, were included in the meta-analysis. Characteristics of these studies are summarized in Table 1. The included studies were made publicly available through PubMed. Moawd et al. conducted a study consisting of 40 children aged 9 to 11 years with post-operative CDH, randomly assigned into two groups. Participants in the study group (n=20) performed inspiratory

Table 1. Characteristics of Studies

Author, year	Inclusion criteria	Exclusion criteria	Sample size	Control	Intervention	Outcomes
Moawd 2020	Age 9 to 11 years BMI of 20 to 25 Diagnosed CDH in the first days of life presenting with respiratory distress, immediate operation after birth	Paraesophageal defect Diaphragmatic eventration Inability to conduct study procedures Serious anomalies	40	Incentive spirometry	Inspiratory muscle training (Threshold IMT Breathing trainer) through a spring-loaded valve device	FVC, FEV_1, maximal $V_{O2,}$ V_E/V_{CO2}, 6-minute walk test (6-MWT), Pediatric Quality of Life (PedsQL) questionnaire score
Azab 2022	Age 10 to 14 years BMI of 20 to 25 Diagnosed CDH in the first days of life presenting with respiratory distress, immediate operation after birth Follow-up care in the pediatric and physical therapy clinic	Physical disability Diaphragmatic eventration Inability to conduct study procedures Cardiac anomalies	32	Chest physiotherapy (chest percussion and vibration)	Chest resistance and expansion exercises	FVC, FEV_1, maximal inspiratory pressure (PImax), thoracic excursion (cm)
Azab 2023	Age 6 to 10 years BMI 20 to 24 Surgically repaired CDH Respiratory symptoms Follow-up care in the pediatric and physical therapy clinic	Abnormal growth Neuromotor disorder Inability to understand procedure Cardiac anomalies	52	Diaphragm strengthening and breathing exercises, aerobic exercises on stationary bicycle, and chest percussion while positioned on prone or side-lying	Virtual reality exercises (jogging, yoga, and twisting and squatting) via Nintendo Wii	FVC, FEV_1, FEV_1/FVC, peak $V_{O2,}$ V_E/V_{CO2}, 6-MWT, PedsQL score

muscle training combined with incentive spirometer training, whereas the control group (n=20) performed only incentive spirometer training. These were done 30 minutes daily, thrice per week, for 12 consecutive weeks.[8] Azab et al. conducted a study in 2022 involving 32 children aged 10 to 14 years with post-operative CDH, randomly assigned to study group (n=16) and control group (n=16). Both groups were exposed to conventional chest physiotherapy for 12 weeks, consisting of chest percussion and vibration for three to five minutes, and placing on prone or side-lying position two to three times each week. The study group, however, underwent an additional regimen of chest resistance and expansion exercises three times per week in those 12 weeks.[7] Lastly, in 2023, Azab et al. conducted a study on 52 CDH survivors aged 6 to 10 years, randomly divided into two groups. The control group (n=26) and the study group (n=26) both underwent diaphragm strengthening and breathing exercises, aerobic exercises via use of a stationary bicycle, and chest percussion while positioned on prone or side-lying, done three times weekly for 12 weeks. After each session, the study group, performed additional 30-minute virtual reality exercises consisting of jogging, yoga, and twisting and squatting using Nintendo Wii.[27] No statistically significant intergroup difference was found in the baseline clinical characteristics of the study groups and control groups pre-intervention in all studies, including pulmonary function tests and duration of hospitalization. Azab et al.[7] and Azab et al.[27] both reported sidedness of the CDH preoperatively, which in both studies did not show statistical difference at baseline between the study and control groups.

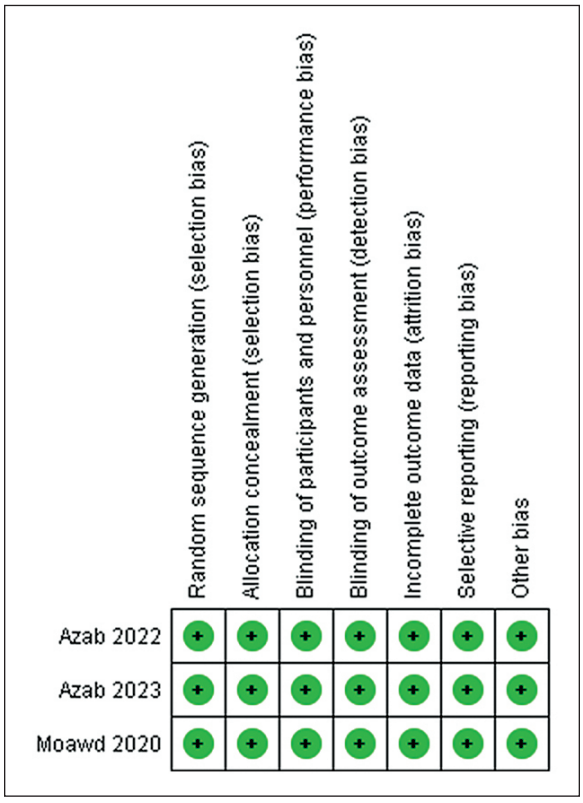

Figure 2. Summary of risk of bias of studies.

The three studies included were shown to be of high quality and have no concerns for selection bias, performance bias, detection bias, attrition bias, and reporting bias. The summary of risk of bias of studies is shown in Figure 2.

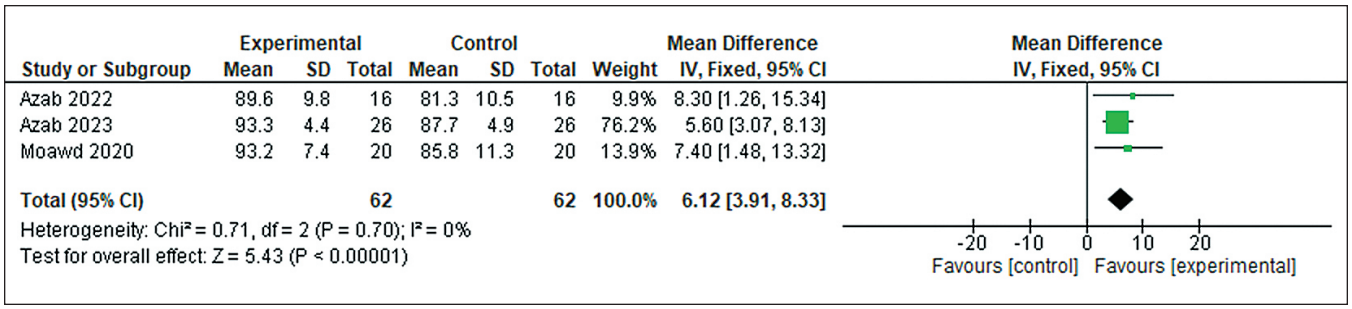

Figure 3. Forest plot on the effect of exercise on FVC.

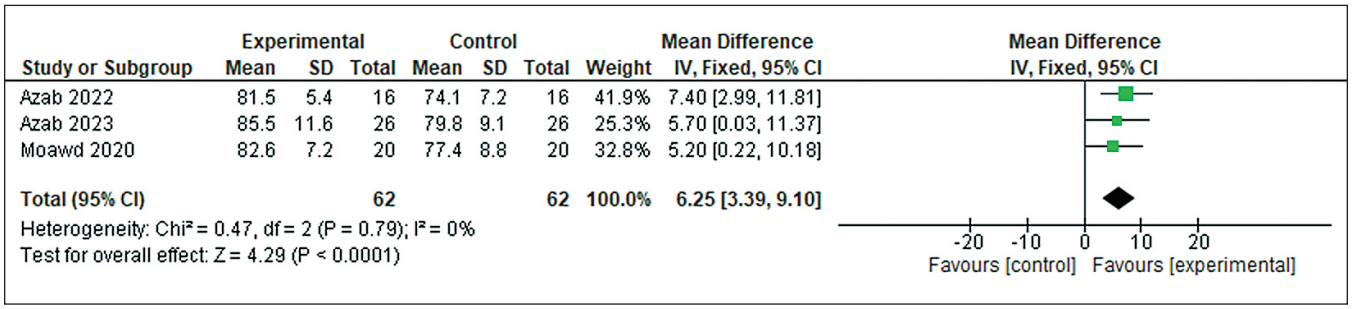

Figure 4. Forest plot on the effect of exercise on FEV_1.

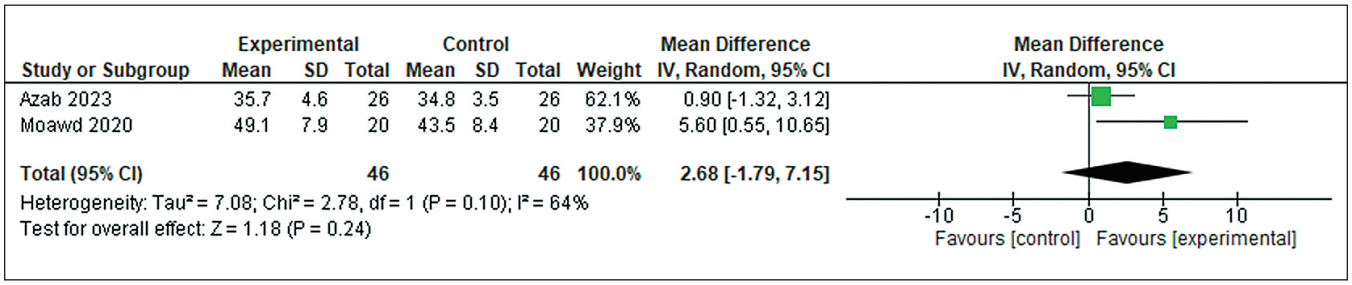

Figure 5. Forest plot on the effect of exercise on maximal oxygen uptake.

Effect of exercise in improving FEV_1, FVC, and FEV_1/FVC in pediatric post-operative CDH patients

Three studies were included which reported the effect of exercise on FVC. The pooled mean difference showed a significantly higher mean FVC after exercise compared to the control group (MD=6.12, 95%CI=3.91 to 8.33, p-value<0.00001). The forest plot on the effect of exercise on FVC is shown in Figure 3.

Three studies were included which reported the effect of exercise on FEV_1. The pooled mean difference showed a significantly higher mean FEV_1 after exercise compared to the control group (MD=6.25, 95%CI=3.39 to 9.10, p-value<0.0001). The forest plot on the effect of exercise on FEV_1 is shown in Figure 4.

A meta-analysis was not done for the outcome of FEV_1/FVC because only one study contained information for this outcome.

Effect of exercise in increasing exercise capacity in pediatric post-operative CDH patients

Two studies were included which reported the effect of exercise on maximal oxygen uptake (peak V_{O2}). The pooled mean difference showed no significant difference in peak V_{O2} (MD=2.68, 95%CI=-1.79 to 7.15, p-value=0.24). The studies were heterogenous (I^2=64%). The forest plot on the effect of exercise on maximal oxygen uptake is shown in Figure 5.

Two studies were included which reported the effect of exercise on the ratio of V_E to V_{CO2}. The pooled mean difference showed no significant difference in lowest V_E/V_{CO2} (MD=-2.08, 95%CI=-2.32 to 1.15, p-value=0.21). The studies were heterogenous (I^2=62%). The forest plot on the effect of exercise on VE/V_{CO2} is shown on Figure 6.

Table 2. Summary of Results of Meta-analysis

Outcome	Mean Difference (95%CI, *p*-value)	Heterogeneity	Certainty assessment using GRADE approach
FVC	MD=6.12 (95%CI=3.91 to 8.33, *p*-value<0.00001)	0%, low	++++ High
FEV$_1$	MD=6.25 (95%CI=3.39 to 9.10, *p*-value<0.0001)	0%, low	++++ High
Maximal oxygen uptake	MD=2.68 (95%CI=-1.79 to 7.15, *p*-value=0.24)	64%, moderate	+++ Moderate
VE/V$_{CO2}$	MD=-2.08 (95%CI=-2.32 to 1.15, *p*-value=0.21)	62%, moderate	+++ Moderate
Quality of life	MD=6.23 (95%CI=3.47 to 8.99, *p*-value<0.0001)	0%, low	++++ High

Table 3. Sensitivity Analysis for FVC

Study removed	MD (95%CI)	I^2
Azab 2022	5.88 (3.55 to 8.21)	0%
Azab 2023	7.77 (3.24 to 12.30)	0%
Moawd 2020	5.91 (3.53 to 8.29)	0%

Table 4. Sensitivity analysis for FEV$_1$

Study removed	MD (95%CI)	I^2
Azab 2022	5.42 (1.68 to 9.16)	0%
Azab 2023	6.43 (3.13 to 9.74)	0%
Moawd 2020	6.76 (3.28 to 10.24)	0%

Effect of exercise in improving quality of life in pediatric post-operative CDH patients

Two studies were included which looked at the effect of exercise on quality of life. The pooled mean difference showed a significantly higher QOL after exercise compared to the control group (MD=6.23, 95%CI=3.47 to 8.99, p-value<0.0001). The forest plot on the effect of exercise on quality of life is shown in Figure 7.

As seen in Table 2, throughout the three trials, the exercise groups' FVC and FEV$_1$ improved statistically significantly when compared to the control groups. Also, significant benefit in higher quality of life scores was observed for the exercise group in two trials. GRADE level of evidence showed high certainty for the outcomes FVC, FEV$_1$, and quality of life given the RCT design and consistency of findings. For the outcomes of maximal oxygen uptake and VE/V$_{CO2}$, the level of evidence was downgraded to moderate because of heterogeneity.

Sensitivity analysis shown on Table 3 and Table 4 demonstrated robustness of findings and consistency of results regardless which study was excluded.

DISCUSSION

The results of the meta-analysis showed statistically significant improvement in FVC and FEV$_1$ in the study groups compared to control groups across the three studies. In the study of Moawd et al.[8], participants who underwent inspiratory muscle training had significant improvement in respiratory function (FVC, p<0.001; FEV$_1$, p=0.002) while

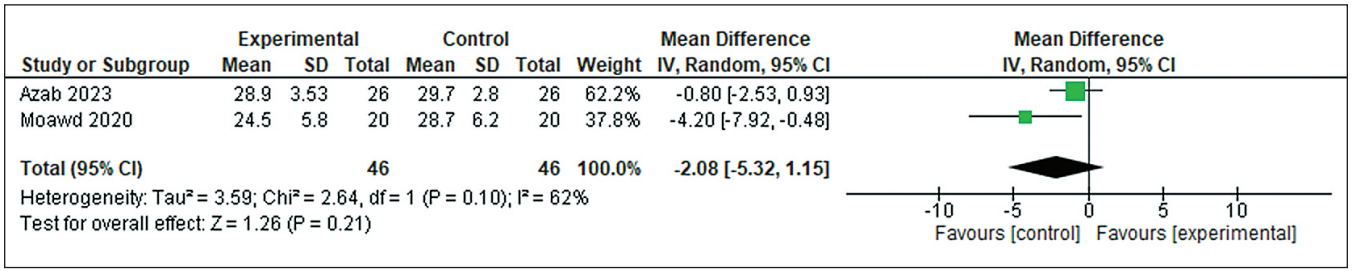

Figure 6. Forest plot on the effect of exercise on VE/V$_{CO2}$.

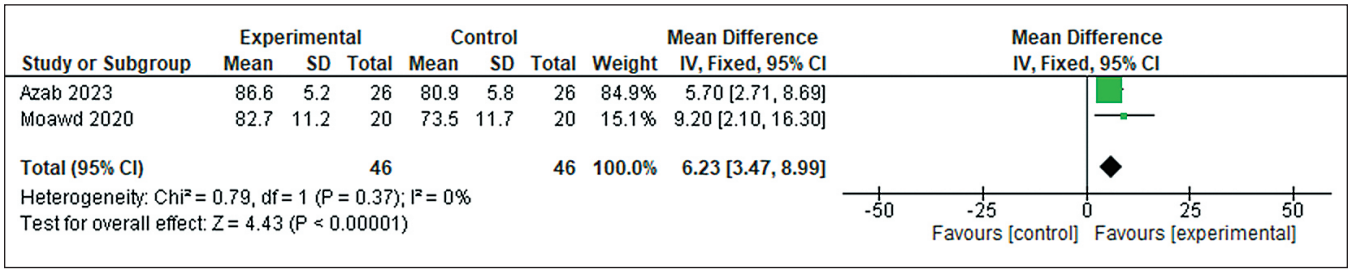

Figure 7. Meta-analysis on the effect of exercise on quality of life.

no significant changes (p>0.05) were seen in the control group. Similarly, participants in the study of Azab et al.[7] that underwent chest resistance training had statistically significant improvement in both parameters (FVC, p=0.005, FEV_1, p=0.001), as well as in the study of Azab et al.[27] in which the study group had pulmonary functions higher than those of the control group (FEV_1, p=0.001, FVC, p=0.0002).

Meta-analysis was not conducted for FEV_1/FVC which was only measured in the study of Azab et al.[27] which showed a significant increase (p=0.003) in the ratio, indicating a decrease in the obstructive nature of the disease for that particular study. Further studies investigating this parameter should be conducted to give more clinical significance to the other outcomes of pulmonary function.

The meta-analysis also revealed no significant difference in peak V_{O2} and $V_E/V_{CO2,}$ indicating no statistically significant improvement in exercise capacity. Peak V_{O2} in cardiopulmonary exercise testing is directly correlated with exercise tolerance, while an increased V_E/V_{CO2} is associated with ventilation-perfusion mismatch.[28]

Quality of life was found to be statistically improved on meta-analysis of the studies by Moawd et al.[8] (p<0.001) and Azab et al.[27] (p<0.001). Both studies used the Pediatric Quality of Life (PedsQL) questionnaire, with responses from parents of the participants, and self-reports for children older than eight years.

The results of the meta-analysis indicate that exercise is effective in improving lung function and quality of life in pediatric CDH survivors. However, despite the favorable results of the studies included in this meta-analysis, certain limitations exist. For all the outcomes studied, there was risk for measurement bias given that performance in lung function device relies on the cooperation and motivation of the child. Another limitation was that long-term outcomes were not assessed in the included studies, hence sustainability of the observed benefits of exercise has not been established. Also, the generalizability and external validity may be constrained by each of the study's small sample size. Future research is recommended to determine the mechanism by which breathing exercises affect physiological markers. Moreover, investigations should be made to determine these improvements are clinically significant in the patients' respiratory symptomatology over a longer period of observation. Furthermore, since there were different exercise regimens presented in each trial, the meta-analysis could not fully explain whether the type of exercise performed can affect the degree of improvement. As such, while exercise showed improvement in lung function and quality of life in post-operative CDH patients and should be recommended in this population, a particular exercise regimen cannot be recommended at this time and should be investigated further. These variations in type of exercise, as well as study setting could have caused the observed moderate heterogeneity among studies. However, given that only two studies were included for the outcomes VE/V_{CO2} and maximal oxygen intake, meta-regression or sensitivity analysis cannot be performed. Nonetheless, given the consistent direction magnitude of effect reported in each study, we are confident on the robustness of our statistical analysis. Finally, the relationship between the pre-operative type of CDH and the degree of improvement after exercise regimen should also be investigated, since traditionally, left-sided CDH implies a better prognosis. Documenting presence of pulmonary hypoplasia and pulmonary hypertension may also aid in determining the effectiveness of exercise regimen for these children. The level of exercise and physical fitness of participants prior to interventions in succeeding studies should also be documented as this may directly affect the improvement of lung function after the interventions.

CONCLUSION

This meta-analysis provided good-quality evidence of the effectiveness of exercise in improving lung function and quality of life in children with pediatric post-operative congenital diaphragmatic hernia. These patients may benefit from exercise regimens in their rehabilitation programs. However, further studies should be done to establish the most effective exercise regimen for this population.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

Funding Source

The study was funded by the authors.

REFERENCES

1. Bush A, Abel R, Chitty L, Harcourt J, Hewitt R, Nicholson AG. Congenital lung disease. In: Bush A, Deterding R, Li A, Ratjen F, Sly P, Zar H, et al, eds. Kendig's disorders of the respiratory tract in children, 9th ed. Philadelphia: Elsevier; 2019. pp. 292-294.
2. Philippine Pediatric Society, Pediatric disease registry program [Internet]. 2020 [cited 2023 Oct]. Available from: https://pps.ivant.com/search.do.
3. Hendrick H, Adzick S. Congenital diaphragmatic hernia in the neonate [Internet]. 2021 [cited 2023 Oct]. Available from: https://www.uptodate.com/contents/congenital-diaphragmatic-hernia-in-the-neonate.
4. Ahlfeld SK. Diaphragmatic hernia. In: Behrman R, Kliegman R, Schor N, Stanton B, Nelson W, eds. Nelson textbook of pediatrics, 21st ed. Philadelphia: Elsevier; 2020. pp. 944-945.
5. Bojanić K, Grizelj R, Dilber D, Šarić D, Vuković J, Pianosi P, et al. Cardiopulmonary exercise performance is reduced in congenital diaphragmatic hernia survivors. Pediatr Pulmonol. 2016 Dec;51(12):1320-9. doi: 10.1002/ppul.23481. PMID: 27228382.
6. Dao D, Hayden L, Buchmiller T, Kharasch V, Kamran A, Smithers C, et al. Longitudinal analysis of pulmonary function in survivors of congenital diaphragmatic hernia. J Pediatr. 2020 Jan;216:158-164.e2. doi: 10.1016/j.jpeds.2019.09.072. PMID: 31704056; PMCID: PMC6917899.

7. Azab A, Abdelbasset W, Alrawaili S, Elsayed A, Hajelbashir M, Kamel F, et al. Effect of chest resistance and expansion exercises on respiratory muscle strength, lung function, and thoracic excursion in children with a post-operative congenital diaphragmatic hernia. Int J Environ Res Public Health. 2022 May 17;19(10):6101. doi: 10.3390/ijerph19106101. PMID: 35627640; PMCID: PMC9142097.
8. Moawd S, Azab A, Ibrahim Z, Verma A, Abdelbasset W. Impacts of respiratory muscle training on respiratory functions, maximal exercise capacity, functional performance, and quality of life in school-aged children with postoperative congenital diaphragmatic hernia. Dis Markers. 2020 Sep 4;2020:8829373. doi: 10.1155/2020/8829373. PMID: 32963638; PMCID: PMC7492875.
9. Kassim Z, Moxham J, Davenport M, Nicolaides K, Greenough A, Rafferty G. Respiratory muscle strength in healthy infants and those with surgically correctable anomalies. Pediatr Pulmonol. 2015 Jan;50(1):71-8. doi: 10.1002/ppul.23007. PMID: 24574153.
10. Dimitriou G, Greenough A, Kavvadia V, Davenport M, Nicolaides K, Moxham J, et al. Diaphragmatic function in infants with surgically corrected anomalies. Pediatr Res. 2003 Oct;54(4):502-8. doi: 10.1203/01.PDR.0000081299.22005.F0. PMID: 12815114.
11. Peetsold M, Heij H, Nagelkerke A, Ijsselstijn H, Tibboel D, Quanjer P, et al. Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia. Eur Respir J. 2009 Nov;34(5):1140-7. doi: 10.1183/09031936.00181408. PMID: 19282341.
12. Chiu P, Sauer C, Mihailovic A, Adatia I, Bohn D, Coates A, et al. The price of success in the management of congenital diaphragmatic hernia: is improved survival accompanied by an increase in long-term morbidity? J Pediatr Surg. 2006 May;41(5):888-92. doi: 10.1016/j.jpedsurg.2006.01.026. PMID: 16677876.
13. Michel F, Baumstarck K, Gosselin A, Coz P, Merrot T, Hassid S, et al. Health-related quality of life and its determinants in children with a congenital diaphragmatic hernia. Orphanet J Rare Dis. 2013 Jun 20;8:89. doi: 10.1186/1750-1172-8-89. PMID: 23786966; PMCID: PMC3718687.
14. Gloeckl R, Marinov B, Pitta F. Practical recommendations for exercise training in patients with COPD. Eur Respir Rev. 2013 Jun 1;22(128):178-86. doi: 10.1183/09059180.00000513. PMID: 23728873; PMCID: PMC9487382.
15. Kozu R, Senjyu H, Jenkins S, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Respiration. 2011;81(3):196-205. doi: 10.1159/000315475. PMID: 20516666.
16. Olenich S, Waterworth G, Badger G, Levy B, Israel E, Langevin H. Flexibility and strength training in asthma: a pilot study. J Asthma. 2018 Dec;55(12):1376-83. doi: 10.1080/02770903.2017.1414236. PMID: 29420095.
17. de Lima F, Pinheiro D, de Carvalho C. Physical training in adults with asthma: An integrative approach on strategies, mechanisms, and benefits. Front Rehabil Sci. 2023 Feb 17;4:1115352. doi: 10.3389/fresc.2023.1115352. PMID: 36873818; PMCID: PMC9982132.
18. Turchetta A, Fintini D, Cafiero G, Calzolari A, Giordano U, Cutrera R, et al. Physical activity, fitness, and dyspnea perception in children with congenital diaphragmatic hernia. Pediatr Pulmonol. 2011 Oct;46(10):1000-6. doi: 10.1002/ppul.21471. PMID: 21520442.
19. Lewis L, Sinha I, Kang S, Lim J, Losty P. Long term outcomes in CDH: Cardiopulmonary outcomes and health related quality of life. J Pediatr Surg. 2022 March;57:501-9. doi: 10.1016/j.jpedsurg.2022.03.020. PMID: 35508437.
20. Miles K, Powell A, Critser P, Hardie W, O'Neil M, Cash M, et al. Long-term exercise and pulmonary function outcomes in a contemporary cohort of children with congenital diaphragmatic hernia. Pediatr Pulmonol. 2023 May;58(5):1471-80. doi: 10.1002/ppul.26348. PMID: 36751101.
21. Toussaint-Duyster L, van der Cammen-van Zijp M, de Jongste J, Tibboel D, Wijnen R, Gischler S, et al. Congenital diaphragmatic hernia and exercise capacity, a longitudinal evaluation. Pediatr Pulmonol. 2019 May;54(5):628-36. doi: 10.1002/ppul.24264. PMID: 30741484; PMCID: PMC6593853.
22. West J, Luks A. Mechanics of breathing. In: West J, Luks A, eds. West's respiratory physiology: the essentials, 10th ed. Philadelphia: Wolters Kluwer; 2016. pp. 109-110.
23. McConnell A, Romer L, Weiner P. Inspiratory muscle training in obstructive lung disease. Breathe. 2005;2:38-49. doi: 10.1183/18106838.0201.38.
24. Wang Q, Yang F, Gao L, Gao W. Effects of inspiratory muscle training and high-intensity interval training on lung function and respiratory muscle function in asthma. Respir Care. 2022 Jul 19:respcare.09813. doi: 10.4187/respcare.09813. PMID: 35853706.
25. Figueiredo R, Azambuja A, Cureau F, Sbruzzi G. Inspiratory muscle training in COPD. Respir Care. 2020 Aug;65(8):1189-201. doi: 10.4187/respcare.07098. PMID: 32209709.
26. Crisafulli E, Costi S, Fabbri L, Clini E. Respiratory muscles training in COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(1):19-25. doi: 10.2147/copd.2007.2.1.19. PMID: 18044062; PMCID: PMC2692111.
27. Azab A, Elnaggar R, Abdelbasset W, Alghadier M, Ahmed A, Alsharidah A, et al. Virtual reality-based exercises' effects on pulmonary functions, cardiopulmonary capacity, functional performance, and quality of life in children with repaired congenital diaphragmatic hernia. Eur Rev Med Pharmacol Sci. 2023 Jul;27(14):6480-8. doi: 10.26355/eurrev_202307_33118. PMID: 37522659.
28. Mezzani A. Cardiopulmonary exercise testing: basics of methodology and measurements. Ann Am Thorac Soc. 2017 Jul;14(Supplement_1):S3-S11. doi: 10.1513/AnnalsATS.201612-997FR. PMID: 28510504.