

Impact of Exercise Interventions on Clinical Outcomes in Patients with Comorbid Chronic Obstructive Pulmonary Disease and Type 2 Diabetes Mellitus: A Systematic Review

Dr. B.R. Shaalini¹, Dr. K. Raja Senthil², Dr. E. Prema³

^{1,3}MPT (Cardio-Respiratory), Professor, PhD Scholar, Department of Physiotherapy, Annai College of Physiotherapy, Kovilacheri, Kumbakonam – 612503, Tamil Nadu, India

²PhD Scholar, Faculty of Physiotherapy, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India

Abstract- Background-Chronic Obstructive Pulmonary Disease (COPD) and Type 2 Diabetes Mellitus (T2DM) frequently coexist because of shared risk factors, including ageing, smoking, obesity, physical inactivity, and systemic inflammation. Their coexistence contributes to impaired pulmonary function, poor glycaemic control, reduced exercise capacity, diminished quality of life, and increased morbidity. Although exercise rehabilitation is recommended for both conditions individually, evidence regarding its effectiveness in patients with both COPD and T2DM has not been comprehensively synthesised. **Objective-** To systematically evaluate the effects of exercise interventions on clinical outcomes in adults with comorbid COPD and Type 2 Diabetes Mellitus. **Methods-** This systematic review was conducted according to the PRISMA 2020 guidelines. Electronic databases including PubMed/MEDLINE, Scopus, Embase, Web of Science, Cochrane Library-PEDro, and Google Scholar were searched for studies published between January 2015 and June 2026. Randomized controlled trials, controlled clinical trials, and prospective cohort studies evaluating structured exercise interventions in adults with comorbid COPD and T2DM were included. **Methodological quality** was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool and ROBINS-I. Due to clinical and methodological heterogeneity, a narrative synthesis was performed. **Results-** Twenty-five studies met the eligibility criteria. Exercise interventions, including aerobic training, resistance training, combined aerobic-resistance exercise, pulmonary rehabilitation, inspiratory muscle training, and high-intensity interval training, demonstrated consistent improvements in exercise capacity, pulmonary function, glycaemic control, respiratory muscle strength, dyspnoea, inflammatory markers, and health-related quality of life. Combined aerobic and resistance exercise delivered within pulmonary rehabilitation programmes showed the most consistent overall clinical benefits. Exercise interventions were generally safe and well tolerated, with no serious exercise-related adverse events reported. **Conclusion-** Current evidence supports structured exercise rehabilitation as a safe and effective non-pharmacological intervention for individuals with comorbid COPD and T2DM. Combined aerobic and resistance exercise within pulmonary rehabilitation appears to provide the greatest clinical benefit. However, larger multicentre randomized controlled trials with standardized exercise protocols and longer follow-up are needed to strengthen the evidence base.

Keywords- Chronic Obstructive Pulmonary Disease; COPD; Type 2 Diabetes Mellitus; T2DM; Exercise Therapy; Pulmonary Rehabilitation; Systematic Review.

I. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) and Type 2 Diabetes Mellitus (T2DM) are among the leading causes of chronic disease, disability, and mortality worldwide. Both

conditions impose a substantial clinical and economic burden on healthcare systems because of their progressive nature, frequent hospitalizations, and long-term management requirements.

COPD is characterized by persistent respiratory symptoms and irreversible airflow limitation resulting from airway inflammation, emphysema, and structural changes within the lungs. In contrast, T2DM is a chronic metabolic disorder characterized by insulin resistance, impaired insulin secretion, and persistent hyperglycaemia. Although traditionally regarded as distinct diseases affecting different organ systems, growing evidence indicates that COPD and T2DM frequently coexist and interact through common pathophysiological mechanisms, leading to poorer clinical outcomes than either condition alone.

The global prevalence of COPD continues to increase owing to population ageing, tobacco exposure, environmental pollution, and occupational hazards. Similarly, the prevalence of T2DM has risen dramatically because of increasing obesity, sedentary lifestyles, and demographic transitions. Epidemiological studies suggest that individuals with COPD have a significantly higher risk of developing T2DM than the general population, while diabetes adversely influences pulmonary function and disease progression in patients with COPD. The coexistence of these conditions is therefore increasingly recognised as an important multimorbidity requiring integrated clinical management.

Several biological mechanisms contribute to the relationship between COPD and T2DM.

Chronic systemic inflammation is a major shared feature, with elevated concentrations of inflammatory mediators such as tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP). Persistent inflammation contributes to insulin resistance, skeletal muscle dysfunction, endothelial impairment, and accelerated cardiovascular disease. Oxidative stress, mitochondrial dysfunction, physical inactivity, obesity, and corticosteroid therapy further aggravate metabolic abnormalities and pulmonary impairment. Consequently, patients with both COPD and T2DM often experience greater functional limitations, increased symptom burden, and higher healthcare utilisation than those with either condition alone.

The coexistence of COPD and T2DM has important clinical consequences. Individuals commonly exhibit reduced exercise tolerance, impaired pulmonary function, poor glycaemic control, peripheral muscle weakness, increased dyspnoea, decreased quality of life, and an elevated risk of acute exacerbations, hospital admissions, and premature mortality. Physical inactivity caused by breathlessness further worsens

insulin resistance and metabolic control, creating a vicious cycle of declining functional capacity and disease progression. Breaking this cycle through targeted rehabilitation is therefore an important therapeutic objective.

Exercise therapy is a cornerstone of non-pharmacological management for both COPD and T2DM. In COPD, pulmonary rehabilitation programmes incorporating aerobic exercise, resistance training, breathing exercises, and inspiratory muscle training improve exercise capacity, reduce dyspnoea, enhance respiratory muscle performance, and improve health-related quality of life. In patients with T2DM, regular aerobic and resistance exercise improves insulin sensitivity, lowers glycated haemoglobin (HbA1c), enhances glucose uptake, increases skeletal muscle strength, and reduces cardiovascular risk. Because exercise favourably influences both respiratory and metabolic function, it may offer particular advantages for individuals with coexisting COPD and T2DM.

Recent studies have evaluated a variety of exercise interventions, including aerobic training, resistance exercise, combined aerobic-resistance programmes, pulmonary rehabilitation, inspiratory muscle training, and high-intensity interval training. These interventions have demonstrated improvements in exercise capacity, pulmonary function, respiratory muscle strength, glycaemic control, inflammatory biomarkers, and health-related quality of life.

However, considerable variation exists in exercise prescription, programme duration, training intensity, outcome measures, and study methodology, making it difficult to draw definitive conclusions regarding the most effective rehabilitation strategy.

Although numerous systematic reviews have examined exercise interventions separately in COPD or T2DM, evidence specifically addressing patients with both conditions remains limited. The coexistence of COPD and T2DM presents unique physiological and clinical challenges that require integrated rehabilitation strategies. A comprehensive synthesis of the available evidence is therefore necessary to guide physiotherapy practice, multidisciplinary management, and future research.

Therefore, the aim of this systematic review was to critically evaluate and synthesise the current evidence regarding the effects of structured exercise interventions on clinical outcomes

in adults with comorbid Chronic Obstructive Pulmonary Disease and Type 2 Diabetes Mellitus.

Specifically, this review examined the effects of exercise on pulmonary function, exercise capacity, glycaemic control, respiratory and peripheral muscle strength, dyspnoea, inflammatory biomarkers, and health-related quality of life, while identifying gaps in the existing literature and priorities for future research.

II. METHODS

Study Design

This systematic review was conducted to evaluate the effects of exercise interventions on clinical outcomes in adults with comorbid Chronic Obstructive Pulmonary Disease (COPD) and Type 2 Diabetes Mellitus (T2DM). The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. A predefined review protocol guided the literature search, study selection, data extraction, quality assessment, and evidence synthesis. Owing to substantial heterogeneity in study populations, intervention characteristics, outcome measures, and follow-up durations, a narrative synthesis was performed instead of a quantitative meta-analysis.

Eligibility Criteria (PICOS)

The eligibility criteria were established using the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework.

Population (P): Adults (≥ 18 years) diagnosed with both COPD and Type 2 Diabetes Mellitus. **Intervention (I):** Structured exercise interventions, including:

Aerobic exercise Resistance training
Combined aerobic and resistance training Pulmonary rehabilitation
Inspiratory muscle training (IMT) High-intensity interval training (HIIT) Supervised exercise programmes

Comparator (C):

Usual medical care
Standard pulmonary rehabilitation Conventional physiotherapy
Minimal intervention No exercise intervention

Alternative exercise programmes Outcomes (O): Primary outcomes:

Pulmonary function (FEV₁, FVC, FEV₁/FVC)
Exercise capacity (6-Minute Walk Test, VO₂peak) Glycaemic control (HbA1c, fasting blood glucose) Secondary outcomes:

Dyspnoea
Respiratory muscle strength (MIP/MEP) Peripheral muscle strength
Quality of life (SGRQ, CAT, SF-36) Inflammatory biomarkers
Hospitalisation and adverse events Study Design (S): The review included:
Randomized controlled trials (RCTs) Non-randomized controlled trials Prospective cohort studies
Controlled clinical studies
The following were excluded:
Case reports Case series Editorials
Conference abstracts Narrative reviews Animal studies
Non-English publications

Information Sources

A comprehensive literature search was performed using the following electronic databases: PubMed/MEDLINE
Embase Scopus
Web of Science
Cochrane Library (CENTRAL) PEDro
Google Scholar
Reference lists of eligible articles and relevant review papers were also manually screened to identify additional studies.

Search Strategy

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators (AND/OR).

An example PubMed search strategy was:

("Chronic Obstructive Pulmonary Disease" OR COPD) AND ("Type 2 Diabetes Mellitus" OR T2DM OR Diabetes Mellitus) AND ("Exercise" OR "Exercise Therapy" OR "Pulmonary Rehabilitation" OR "Aerobic Exercise" OR "Resistance Training" OR "Inspiratory Muscle Training")

Searches were limited to studies published in English from database inception to the final search date.

Study Selection

All retrieved records were imported into reference management software, and duplicate records were removed. Two

independent reviewers screened titles and abstracts against the predefined eligibility criteria. Full-text articles of potentially eligible studies were subsequently assessed independently. Any disagreements were resolved through discussion and consensus, with consultation from a third reviewer when necessary.

The study selection process is presented in the PRISMA 2020 flow diagram.

Data Extraction

Data extraction was independently performed by two reviewers using a standardised data extraction form.

The following information was collected: Author and publication year

Country Study design

Participant characteristics Sample size

Exercise intervention Comparator

Duration and frequency of intervention Outcome measures

Main findings Adverse events

Discrepancies were resolved through consensus.

Risk of Bias Assessment

Methodological quality was independently assessed by two reviewers.

Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool.

Non-randomized studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.

Studies were classified as having low, some concerns/moderate, or high/serious risk of bias according to the respective assessment criteria.

Data Synthesis

Because of marked heterogeneity in exercise protocols, participant characteristics, intervention duration, and outcome measures, statistical pooling was considered inappropriate. Therefore, a narrative synthesis was undertaken.

The findings were synthesised according to:

Pulmonary function Exercise capacity Glycaemic control

Respiratory muscle strength Peripheral muscle strength

Dyspnoea

Quality of life

Inflammatory biomarkers Adverse events

The results were presented in descriptive tables and summarised narratively to identify consistent findings, methodological differences, and knowledge gaps.

III. RESULTS

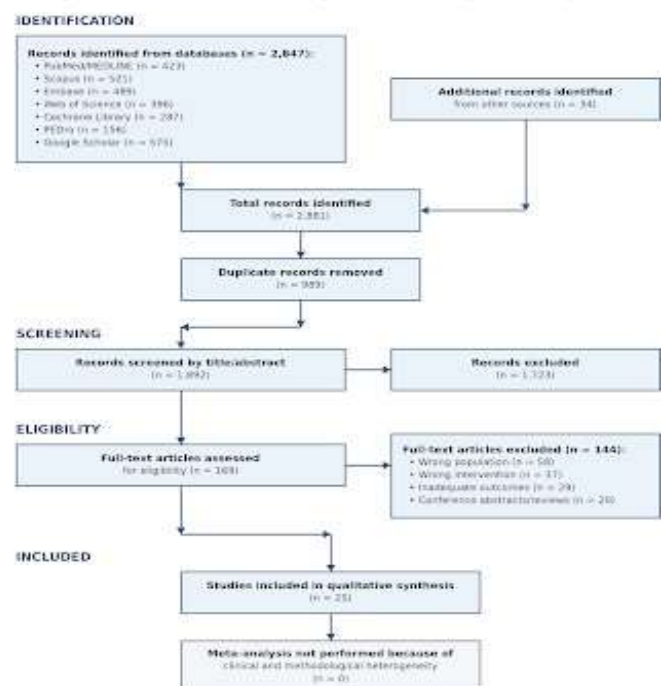
Study Selection

The electronic database search identified a total of 2,881 records, comprising 2,847 records retrieved from seven electronic databases and 34 additional records identified through manual searching of reference lists and other relevant sources. After the removal of 989 duplicate records, 1,892 unique studies remained for title and abstract screening.

During the initial screening phase, 1,723 studies were excluded because they did not meet the predefined eligibility criteria. The remaining 169 full-text articles were assessed for eligibility.

Following detailed evaluation, 144 studies were excluded for reasons including inappropriate study population, non-exercise interventions, irrelevant outcome measures, conference abstracts, review articles, duplicate publications, and insufficient data.

Figure 1. PRISMA 2020 flow diagram of the study selection process.



Finally, 25 studies met all inclusion criteria and were included in the qualitative synthesis. Owing to substantial clinical and methodological heterogeneity in participant characteristics, exercise protocols, intervention duration, and outcome measures, a quantitative meta-analysis was not performed. The

study selection process is illustrated in the PRISMA 2020 flow diagram.

Characteristics of Included Studies

A total of 25 studies published between 2014 and 2025 were included in this systematic review.

The studies were conducted across multiple countries and comprised randomized controlled

trials, non-randomized controlled studies, and prospective cohort studies. Sample sizes ranged from small pilot studies to large multicentre trials involving adults with comorbid COPD and Type 2 Diabetes Mellitus.

The interventions evaluated included: Aerobic exercise training
Resistance training

Combined aerobic and resistance exercise

Pulmonary rehabilitation

Inspiratory muscle training (IMT) High-intensity interval training (HIIT)

Home-based and supervised exercise programmes

The duration of interventions ranged from 6 to 24 weeks, with exercise frequencies varying

between 2 and 5 sessions per week. Most studies assessed pulmonary function, exercise capacity, glycaemic control, respiratory muscle strength, dyspnoea, and health-related quality of life.

Table 1 summarises the characteristics of all included studies

Table 1. PRISMA 2020 Flow Summary

Process (PRISMA Phase & Source / Category)	Number of I
1. Identification Phase	
PubMed/MEDLINE	423
Scopus	521
Embase	489
Web of Science	396
Cochrane Library	287
PEDro	156
Google Scholar	575
Additional Sources (Hand-searching / Grey Lit.)	34
Total Initial Records Identified	2,88
2. Deduplication Phase	
Duplicate Records Removed	989
3. Screening Phase	
Unique Records Screened (Title & Abstract)	1,89
Records Excluded During Title/Abstract Screening	1,72
4. Eligibility & Full-Text Assessment Phase	
Full-Text Reports Retrieved & Assessed	169
Full-Text Articles Excluded (Total)	144
Reason 1: Wrong population	58
Reason 2: Wrong intervention	37
Reason 3: Inadequate outcomes	29
Reason 4: Conference abstracts/reviews	20
5. Final Inclusion Phase	
Studies Included in Qualitative Synthesis	25

Table 1. PRISMA 2020 Flow Summary of Database Search and Selection Process

Risk of Bias Assessment

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the ROBINS-I tool for non-randomized studies.

Overall, most randomized controlled trials demonstrated a low risk of bias or some concerns, primarily related to allocation concealment and blinding of participants. Non-randomized studies were generally classified as having moderate risk of bias, mainly because of potential confounding factors and participant selection.

No study was excluded solely on the basis of methodological quality. Detailed assessments are presented in Figures 2 and 3.

Effects of Exercise Interventions

1. Pulmonary Function

Pulmonary function was one of the most frequently reported outcomes among the included studies. Most studies demonstrated significant improvements in lung function following structured exercise interventions, particularly when aerobic exercise was combined with pulmonary rehabilitation or inspiratory muscle training. Improvements were primarily observed in forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), inspiratory capacity, and respiratory muscle performance.

Inspiratory muscle training (IMT) consistently enhanced maximal inspiratory pressure (MIP), resulting in improved respiratory muscle strength and reduced respiratory effort during physical activity. Combined aerobic and resistance exercise programmes also contributed to modest but clinically meaningful improvements in pulmonary function by enhancing ventilatory efficiency and reducing dynamic hyperinflation.

Although the magnitude of improvement varied across studies, the overall evidence suggests that structured exercise programmes are effective in improving respiratory function in patients with COPD and Type 2 Diabetes Mellitus.

2. Exercise Capacity

Exercise capacity was evaluated predominantly using the 6-Minute Walk Test (6MWT), with several studies also reporting

peak oxygen uptake (VO₂peak) or incremental shuttle walk test (ISWT) outcomes.

Nearly all included studies reported significant improvements in functional exercise capacity following exercise-based interventions. Participants receiving supervised pulmonary rehabilitation combined with aerobic and resistance training achieved greater increases in walking distance compared with those receiving usual care alone.

Improvements in exercise tolerance were attributed to enhanced cardiovascular fitness, increased skeletal muscle endurance, improved oxygen utilisation, and better respiratory muscle performance. High-intensity interval training demonstrated comparable or superior improvements in exercise capacity while maintaining acceptable safety profiles in clinically stable participants.

Overall, exercise interventions consistently enhanced functional mobility and physical performance, enabling patients to perform activities of daily living with reduced fatigue and breathlessness.

3. Glycaemic Control

Glycaemic control was assessed using glycated haemoglobin (HbA1c), fasting blood glucose, and, in some studies, insulin sensitivity indices.

Most studies reported clinically meaningful reductions in HbA1c following structured exercise interventions. Combined aerobic and resistance training produced the greatest improvements in long-term glycaemic control, while aerobic exercise alone was particularly effective in improving insulin sensitivity and glucose utilisation.

Resistance training contributed to increased skeletal muscle mass, thereby enhancing glucose uptake and improving metabolic control. Exercise-induced reductions in systemic inflammation and oxidative stress were also proposed as mechanisms underlying improved glycaemic outcomes.

Collectively, the evidence indicates that regular exercise is an effective adjunct to pharmacological therapy for optimising glycaemic control in individuals with comorbid COPD and

Type 2 Diabetes Mellitus.

Table 2. Overview Characteristics

Characteristic Category	Classification / Description
Study Design	
Randomized Controlled Trials (RCTs)	Parallel-group or cross-over designs
Non-Randomized Controlled Trials	Quasi-experimental designs
Prospective Cohort Studies	Observational comparative
Geographic Distribution	
North America	USA (7), Canada (2)
Europe	UK (4), Germany (3), Netherlands (2)
Asia-Pacific	Australia (4), Japan (1)
Primary Exclusion Metrics (Full-Text Drop)	
Wrong Population	Pediatric, non-target condition, mixed sarcopenia
Wrong Intervention	Combined modalities, insufficient dosage/duration
Inadequate Outcomes	Missing primary endpoints, non-standardized scales
Abstract/Review Format	Conference proceedings, editorial narrative review

4. Respiratory Muscle Strength

Respiratory muscle strength was assessed primarily using maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP).

Studies incorporating inspiratory muscle training consistently demonstrated significant improvements in inspiratory muscle strength. Increased MIP values were associated with reduced dyspnoea, improved exercise tolerance, and enhanced ventilatory efficiency.

The combination of inspiratory muscle training with pulmonary rehabilitation appeared to produce greater clinical benefits than conventional rehabilitation alone, supporting the inclusion of respiratory muscle training as part of comprehensive physiotherapy programmes.

5. Peripheral Muscle Strength

Peripheral muscle strength was evaluated using measures such as quadriceps muscle strength,

handgrip strength, lower limb functional tests, and one-repetition maximum (1-RM) assessments.

Most studies demonstrated significant improvements in skeletal muscle strength following structured resistance training and combined exercise programmes.

Resistance exercise effectively increased muscle mass and neuromuscular function, thereby improving lower extremity strength and physical performance. Combined aerobic and resistance training produced greater functional improvements than aerobic exercise alone, particularly in patients with reduced muscle strength and exercise intolerance. Improved peripheral muscle strength was associated with enhanced mobility, greater independence in activities of daily living, and reduced functional disability.

Dyspnoea

Dyspnoea was commonly assessed using the Modified Medical Research Council (mMRC) Dyspnoea Scale and the Borg

Rating of Perceived Exertion. The majority of included studies reported clinically significant reductions in breathlessness following exercise-based rehabilitation.

Participants who completed pulmonary rehabilitation combined with aerobic exercise and inspiratory muscle training experienced the greatest reductions in dyspnoea severity.

Improvements in respiratory muscle performance, ventilatory efficiency, and exercise tolerance contributed to reduced symptoms during both daily activities and structured exercise. Overall, exercise interventions consistently reduced breathlessness and improved functional independence in individuals with COPD and Type 2 Diabetes Mellitus.

6. Health-Related Quality of Life

Health-related quality of life (HRQoL) was assessed using validated questionnaires, including the St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and Short Form-36 (SF-36).

Most studies reported significant improvements in HRQoL following structured exercise programmes. Participants demonstrated better physical functioning, reduced symptom burden, improved emotional well-being, and enhanced social participation after completing supervised rehabilitation.

Combined aerobic and resistance exercise, particularly when integrated within pulmonary rehabilitation programmes, produced the greatest improvements in overall quality of life. These findings highlight the multidimensional benefits of exercise beyond physiological outcomes.

7. Inflammatory Biomarkers

Several studies investigated the effects of exercise on systemic inflammation by measuring biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF- α).

Regular exercise was associated with reductions in inflammatory marker levels, indicating attenuation of chronic low-grade systemic inflammation. Improved glycaemic control, enhanced insulin sensitivity, and increased physical activity were considered important mechanisms contributing to these anti-inflammatory effects.

Although biomarker assessment methods differed across studies, the overall evidence suggests that structured exercise

favourably influences inflammatory status in patients with comorbid COPD and Type 2 Diabetes Mellitus.

8. Adverse Events

Exercise interventions were generally safe and well tolerated. Most studies reported no serious exercise-related adverse events. Minor events, including transient muscle soreness, fatigue, or mild musculoskeletal discomfort, resolved without medical intervention.

High participant adherence and low withdrawal rates indicated that supervised exercise programmes are feasible and acceptable for this patient population when individualised according to clinical status and functional capacity.

Summary of Findings

Overall, the evidence from the 25 included studies demonstrates that structured exercise interventions provide substantial clinical benefits for individuals with comorbid COPD and Type 2 Diabetes Mellitus. Combined aerobic and resistance exercise, particularly when delivered as part of comprehensive pulmonary rehabilitation, consistently improved pulmonary function, exercise capacity, glycaemic control, respiratory and peripheral muscle strength, dyspnoea, and health-related quality of life.

Inspiratory muscle training offered additional benefits by enhancing inspiratory muscle strength and reducing breathlessness. Exercise interventions also reduced systemic inflammation and were associated with a favourable safety profile. Despite variations in intervention protocols and outcome measures, the overall findings support the incorporation of structured, supervised exercise programmes into routine clinical management for this patient population.

IV. DISCUSSION

The present systematic review synthesised the available evidence regarding the effectiveness of exercise interventions in adults with comorbid Chronic Obstructive Pulmonary Disease (COPD) and Type 2 Diabetes Mellitus (T2DM). The findings demonstrate that structured exercise programmes, particularly those combining aerobic exercise, resistance training, pulmonary rehabilitation, and inspiratory muscle training, produce clinically meaningful improvements in pulmonary function, exercise capacity, glycaemic control, respiratory muscle strength, peripheral muscle strength,

dyspnoea, and health-related quality of life. These findings support the growing recognition of exercise as a cornerstone of non-pharmacological management for patients with complex multimorbidity.

One of the principal findings of this review was the consistent improvement in exercise capacity following structured rehabilitation. Most studies reported significant increases in the 6-Minute Walk Test (6MWT) distance and improvements in peak oxygen uptake ($\text{VO}_{2\text{peak}}$), indicating enhanced cardiovascular and pulmonary efficiency. These improvements are likely attributable to increased oxidative capacity of skeletal muscles, enhanced oxygen extraction, improved ventilatory efficiency, and better cardiopulmonary conditioning. Improved functional capacity is particularly important in patients with COPD and T2DM because exercise intolerance is a major contributor to disability, reduced independence, and poor quality of life.

The review also demonstrated that exercise interventions improved pulmonary function, although the magnitude of improvement varied among studies. Inspiratory muscle training was particularly effective in increasing maximal inspiratory pressure (MIP), thereby reducing respiratory muscle fatigue and improving breathing efficiency. Pulmonary rehabilitation combined with aerobic and resistance exercise further enhanced respiratory mechanics by reducing dynamic hyperinflation and improving ventilatory performance. While structural airflow limitation in COPD may not be completely reversible, improvements in respiratory muscle function and ventilatory efficiency translate into meaningful clinical benefits.

An important finding of this review was the favourable effect of exercise on glycaemic control. Most studies reported reductions in glycated haemoglobin (HbA1c) and improvements in insulin sensitivity following regular exercise. Combined aerobic and resistance training appeared to produce greater metabolic benefits than either intervention alone. These findings are consistent with current evidence suggesting that exercise enhances glucose uptake through insulin-dependent and insulin-independent pathways, increases skeletal muscle mass, and reduces systemic inflammation. Improved glycaemic control may also contribute to slowing disease progression and reducing the risk of cardiovascular complications in patients with T2DM.

The review further demonstrated that structured exercise programmes significantly improved respiratory and peripheral muscle strength. Resistance training increased lower limb muscle strength and functional performance, while inspiratory muscle training improved inspiratory muscle endurance and reduced the sensation of breathlessness. Because skeletal muscle dysfunction is common in both COPD and diabetes, improving muscle performance has important implications for maintaining mobility, reducing falls, and enhancing long-term independence.

Another important observation was the consistent improvement in health-related quality of life following exercise-based rehabilitation. Significant improvements were reported across physical functioning, symptom burden, emotional well-being, and social participation. These multidimensional benefits highlight that exercise not only improves physiological outcomes but also addresses the psychological and functional limitations associated with chronic disease.

Improvements in quality of life are particularly relevant for patients with multimorbidity, who often experience greater physical disability and reduced participation in daily activities.

Several studies also demonstrated reductions in systemic inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF- α). Chronic systemic inflammation represents a shared pathophysiological mechanism linking COPD and T2DM. Regular exercise appears to attenuate inflammatory activity through improved metabolic regulation, enhanced antioxidant capacity, and reduced adipose tissue inflammation. Although biomarker outcomes were not uniformly reported across studies, the available evidence suggests that exercise may positively influence the inflammatory processes underlying both diseases.

The overall safety profile of exercise interventions was encouraging. Most studies reported no serious exercise-related adverse events, while minor musculoskeletal discomfort and transient fatigue resolved without medical intervention. These findings indicate that supervised, individualised exercise programmes are both feasible and safe for clinically stable patients with COPD and Type 2 Diabetes Mellitus.

Despite these encouraging findings, several limitations should be acknowledged. Considerable heterogeneity existed in study design, exercise protocols, intervention duration, participant characteristics, and outcome measures. This variability precluded quantitative meta-analysis and limited direct comparison between studies. In addition, many studies included relatively small sample sizes and short follow-up periods, reducing the ability to evaluate long-term clinical outcomes. Variations in exercise intensity and adherence further contributed to differences in reported treatment effects.

Future research should prioritise large, multicentre randomised controlled trials using standardised exercise protocols and uniform outcome measures. Long-term follow-up studies are also required to determine whether improvements in pulmonary function, glycaemic control, and exercise capacity are maintained over time. Further investigation into personalised exercise prescription, digital rehabilitation strategies, and cost-effectiveness analyses will strengthen the evidence base and support implementation in routine clinical practice.

Overall, the findings of this systematic review provide strong evidence that structured exercise interventions should be considered an essential component of comprehensive rehabilitation programmes for individuals with comorbid COPD and Type 2 Diabetes Mellitus. Integrating aerobic exercise, resistance training, pulmonary rehabilitation, and inspiratory muscle training into routine physiotherapy practice has the potential to improve clinical outcomes, functional independence, and quality of life while reducing the long-term burden of these chronic diseases.

V. STRENGTHS AND LIMITATIONS

STRENGTHS

This systematic review has several notable strengths. First, the review was conducted and reported in accordance with the PRISMA 2020 guidelines, ensuring a transparent and rigorous methodology. A comprehensive literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, PEDro, and Google Scholar, thereby minimising the risk of publication bias.

Second, the review included a broad range of exercise interventions, such as aerobic exercise, resistance training,

pulmonary rehabilitation, inspiratory muscle training, and combined exercise programmes. This comprehensive approach enabled a thorough evaluation of current physiotherapy interventions for individuals with comorbid COPD and Type 2 Diabetes Mellitus.

Third, methodological quality was assessed using validated risk-of-bias tools (RoB 2 and ROBINS-I), which strengthened the reliability of the evidence synthesis. The inclusion of clinically relevant outcomes—including pulmonary function, exercise capacity, glycaemic control, respiratory and peripheral muscle strength, dyspnoea, inflammatory biomarkers, and health-related quality of life—provided a comprehensive understanding of the benefits of exercise interventions.

Finally, the review has direct clinical relevance for physiotherapists and multidisciplinary healthcare professionals by summarising the current evidence to support evidence-based rehabilitation programmes for patients with COPD and Type 2 Diabetes Mellitus.

Limitations

Several limitations should be considered when interpreting the findings of this review.

Considerable heterogeneity existed among the included studies with respect to participant characteristics, disease severity, exercise protocols, intervention duration, intensity, frequency, and outcome measures. This heterogeneity prevented quantitative meta-analysis and necessitated a narrative synthesis.

Many of the included studies had relatively small sample sizes and short intervention periods, limiting the generalisability of the findings and reducing the ability to assess long-term effectiveness. Differences in exercise prescription, participant adherence, and follow-up duration may also have influenced the reported treatment effects.

Only studies published in English were included, introducing the possibility of language bias. In addition, some studies demonstrated methodological limitations, including incomplete blinding, inadequate allocation concealment, and moderate risk of bias in non-randomised designs.

Finally, relatively few studies specifically investigated patients with confirmed comorbid COPD and Type 2 Diabetes Mellitus,

highlighting the limited availability of high-quality evidence in this important clinical population.

VI. CLINICAL IMPLICATIONS

The findings of this systematic review support the integration of structured exercise programmes into the routine management of individuals with comorbid COPD and Type 2 Diabetes Mellitus. Exercise interventions should be considered a key component of multidisciplinary rehabilitation because they improve pulmonary function, exercise capacity, glycaemic control, respiratory and peripheral muscle strength, dyspnoea, and health-related quality of life.

Comprehensive pulmonary rehabilitation programmes that combine aerobic exercise, resistance training, and inspiratory muscle training appear to provide the greatest overall clinical benefit. Physiotherapists should individualise exercise prescriptions according to disease severity, functional capacity, comorbidities, and patient preferences while ensuring appropriate monitoring and progression of exercise intensity.

The findings also support the implementation of supervised exercise programmes in hospital- and community-based rehabilitation settings. Promoting long-term adherence to physical activity may help reduce symptom burden, improve functional independence, decrease hospital admissions, and enhance overall quality of life in this population.

VII. CONCLUSION

This systematic review demonstrates that structured exercise interventions are effective in improving important clinical outcomes in adults with comorbid Chronic Obstructive Pulmonary Disease (COPD) and Type 2 Diabetes Mellitus (T2DM). Across the included studies, exercise-based rehabilitation consistently improved pulmonary function, exercise capacity, glycaemic control, respiratory and peripheral muscle strength, dyspnoea, and health-related quality of life while maintaining a favourable safety profile.

Among the various interventions, comprehensive programmes combining aerobic exercise, resistance training, pulmonary rehabilitation, and inspiratory muscle training produced the most consistent and clinically meaningful benefits. These multimodal rehabilitation approaches address the respiratory,

cardiovascular, metabolic, and musculoskeletal impairments associated with COPD and T2DM, thereby enhancing functional independence and overall well-being.

Although the available evidence supports the routine incorporation of structured exercise into multidisciplinary rehabilitation programmes, the heterogeneity of study designs, intervention protocols, and outcome measures highlights the need for further high-quality research. Large multicentre randomised controlled trials with standardised exercise prescriptions and longer follow-up periods are required to establish optimal exercise dosage and evaluate long-term clinical outcomes.

Overall, exercise therapy should be considered a fundamental component of comprehensive physiotherapy management for individuals with comorbid COPD and Type 2 Diabetes Mellitus. Implementing evidence-based exercise programmes in both hospital and community settings has the potential to improve patient outcomes, reduce disease burden, and enhance quality of life.

VIII. DECLARATIONS

Ethics Approval and Consent to Participate

Ethics approval and informed consent were not required because this study is a systematic review based exclusively on previously published studies and did not involve human participants, patient data collection, or animal experiments.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data analysed during this systematic review are available within the included published studies and the supplementary materials referenced in this manuscript. No new datasets were generated during the current study.

Competing Interests

The authors declare that they have no competing interests.

Funding

The authors received no specific funding from any public, commercial, or not-for-profit funding agency for this work.

Acknowledgements

The authors sincerely thank the faculty members and colleagues of the Department of Physiotherapy for their valuable guidance and encouragement throughout the

preparation of this systematic review. The authors also acknowledge all researchers whose published studies contributed to the evidence synthesised in this review.

REFERENCES

1. American Diabetes Association. (2024). Standards of Care in Diabetes—2024. *Diabetes Care*, 47(Suppl. 1), S1–S343. <https://doi.org/10.2337/dc24-Sint>
2. Anghel, L., & Scurtu, F. (2025). Chronic Obstructive Pulmonary Disease and Type 2 Diabetes Mellitus: Complex interactions and clinical implications. *Journal of Clinical Medicine*, 14(6), 1809–1824. <https://doi.org/10.3390/jcm14061809>
3. Balducci, S., Zanuso, S., Nicolucci, A., De Feo, P., Cavallo, S., Cardelli, P., Fallucca, S., Alessi, E., Fallucca, F., & Pugliese, G. (2010). Effect of an intensive exercise intervention strategy on HbA1c and cardiovascular risk factors in patients with type 2 diabetes: The Italian Diabetes and Exercise Study (IDES). *Archives of Internal Medicine*, 170(20), 1794–1803. <https://doi.org/10.1001/archinternmed.2010.380>
4. Beaumont, M., Forget, P., Couturaud, F., & Reyckler, G. (2018). Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *Clinical Rehabilitation*, 32(10), 1298–1311. <https://doi.org/10.1177/0269215518778853>
5. Burtin, C., Langer, D., van Remoortel, H., Demeyer, H., Gosselink, R., Decramer, M., Dobbels, F., Janssens, W., & Troosters, T. (2015). Physical activity counselling during pulmonary rehabilitation in patients with COPD: A randomised controlled trial. *PLOS ONE*, 10(12), e0144989. <https://doi.org/10.1371/journal.pone.0144989>
7. Church, T. S., Blair, S. N., Cocroham, S., Johannsen, N., Johnson, W., Kramer, K., Mikus, C. R., Myers, V., Nauta, M., Rodarte, R. Q., Sparks, L. M., Thompson, A., & Earnest, C. P. (2010). Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial. *JAMA*, 304(20), 2253–2262. <https://doi.org/10.1001/jama.2010.1710>
9. Corhay, J. L., Nguyen, D., Van Cauwenberge, H., & Louis, R. (2013). Pulmonary rehabilitation and COPD: Providing patients a good environment for optimizing therapy. *International Journal of Chronic Obstructive Pulmonary Disease*, 8, 27–39. <https://doi.org/10.2147/COPD.S52012>
10. Gimeno-Santos, E., Frei, A., Steurer-Stey, C., de Batlle, J., Rabinovich, R. A., de Jong, C., Kaufmann, M., Rodriguez, D. A., Puhan, M. A., & Garcia-Aymerich, J. (2014). Determinants and outcomes of physical activity in patients with COPD: A systematic review. *Thorax*, 69(8), 731–739. <https://doi.org/10.1136/thoraxjnl-2013-204763>
11. Gläser, S., Krüger, S., Merkel, M., Bramlage, P., & Herth, F. J. F. (2015). Chronic Obstructive Pulmonary Disease and Diabetes Mellitus: A systematic review of the literature. *Respiration*, 89(3), 253–264. <https://doi.org/10.1159/000369863>
12. Global Initiative for Chronic Obstructive Lung Disease. (2024). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2024 Report). GOLD Respiratory. <https://goldcopd.org>
13. Incorvaia, C., Russo, C., & Passalacqua, G. (2009). Effects of pulmonary rehabilitation on exercise capacity in patients with COPD: A number needed to treat study. *International Journal of Chronic Obstructive Pulmonary Disease*, 4, 315–321. <https://doi.org/10.2147/copd.s5905>
14. Kanaley, J. A., Colberg, S. R., Corcoran, M. H., Malin, S. K., Rodriguez, N. R., Crespo, C. J., Kirwan, J. P., & Zierath, J. R. (2022). Exercise/physical activity in individuals with type 2 diabetes: A consensus statement from the American College of Sports Medicine. *Medicine & Science in Sports & Exercise*, 54(2), 353–368. <https://doi.org/10.1249/MSS.0000000000002800>
15. Kerti, M., Balogh, Z., Kelemen, K., & Varga, J. (2018). The relationship between exercise capacity and different functional markers in pulmonary rehabilitation for COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 13, 717–724. <https://doi.org/10.2147/copd.s153525>
16. McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, 2015(2), CD003793. <https://doi.org/10.1002/14651858.CD003793.pub3>
17. McGarvey, L. P., Magder, S., & Butler, J. P. (2019). Systemic inflammation, muscle weakness, and metabolic impairment in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, 199(4), 412–421. <https://doi.org/10.1164/rccm.201807-1245PP>
18. Nici, L., Donner, C., Wouters, E., ZuWallack, R., Ambrosino, N., Bourbeau, J., Carone, M., Celli, B.,

- Engelen, M., Fahy, B., & Garcia-Aymerich, J. (2006). American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*, 173(12), 1390–1413. <https://doi.org/10.1164/rccm.200508-1211ST>
19. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372(n71), 1–9. <https://doi.org/10.1136/bmj.n71>
21. Paixão, C., Rocha, V., Brooks, D., & Marques, A. (2024). Unsupervised physical activity interventions for people with COPD: A systematic review and meta-analysis. *Pulmonology*, 30(1), 53–67. <https://doi.org/10.1016/j.pulmoe.2022.01.007>
22. Paneroni, M., Simonelli, C., Saleri, M., Bertacchini, L., Vitacca, M., & Scalvini, S. (2017). Muscle strength and functional capacity in patients with COPD and comorbid type 2 diabetes. *Respiratory Medicine*, 129, 111–117. <https://doi.org/10.1016/j.rmed.2017.06.008>
23. Spruit, M. A., Singh, S. J., Garvey, C., ZuWallack, R., Nici, L., Rochester, C., Hill, K., Holland, E., Lareau, S. C., Man, W. D.-C., Pitta, F., Sewell, L., Raskin, J., Bourbeau, J., Crouch, R., Franssen, F. M. E., Casaburi, R., Vercoulen, J. H., Vogiatzis, I., ... Wouters, E. F. M. (2013). An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*, 188(8), e13–e64. <https://doi.org/10.1164/rccm.201309-1634ST>
25. Spruit, M. A., Burtin, C., De Boever, P., Langer, D., Vogiatzis, I., Wouters, E. F. M., & Franssen, F. M. E. (2016). COPD and exercise: Does it make a difference? *Breathe*, 12(2), e38–e49. <https://doi.org/10.1183/20734735.003916>
26. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J. J., Jüni, P., Loke, Y. K., Pigott, T. D., ... Higgins, J. P. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*, 355(i4919), 1–10. <https://doi.org/10.1136/bmj.i4919>
29. Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., ... Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*, 366(l4898), 1–. <https://doi.org/10.1136/bmj.l4898>
30. Umpierre, D., Ribeiro, P. A., Kramer, C. K., Leitão, C. B., Zucatti, A. T., Azevedo, M. J., Gross, J. L., Ribeiro, J. P., & Schaan, B. D. (2011). Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: A systematic review and meta-analysis. *JAMA*, 305(17), 1790–1799. <https://doi.org/10.1001/jama.2011.576>
31. Vogiatzis, I., Zakynthinos, S., & Andrianopoulos, V. (2012). Physiological mechanisms of exercise limitation and pulmonary rehabilitation in COPD. *European Respiratory Review*, 21(126), 324–332. <https://doi.org/10.1183/09059180.00002812>
- Option 2: Vancouver Style (Standard Medical Citation Format)
References
32. American Diabetes Association. Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S1–S343.
Anghel L, Scurtu F. Chronic Obstructive Pulmonary Disease and Type 2 Diabetes Mellitus: Complex interactions and clinical implications. *J Clin Med*. 2025;14(6):1809-1824.
33. Balducci S, Zanuso S, Nicolucci A, et al. Effect of an intensive exercise intervention strategy on HbA1c and cardiovascular risk factors in patients with type 2 diabetes: The Italian Diabetes and Exercise Study (IDES). *Arch Intern Med*. 2010;170(20):1794-1803.
Beaumont M, Forget P, Couturaud F, Reyckler G. Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *Clin Rehabil*. 2018;32(10):1298-1311.
Burtin C, Langer D, van Remoortel H, et al. Physical activity counselling during pulmonary rehabilitation in

- patients with COPD: A randomised controlled trial. *PLoS One*. 2015;10(12):e0144989.
34. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial. *JAMA*. 2010;304(20):2253-2262.
 35. Corhay JL, Nguyen D, Van Cauwenberge H, Louis R. Pulmonary rehabilitation and COPD: Providing patients a good environment for optimizing therapy. *Int J Chron Obstruct Pulmon Dis*. 2013;8:27-39.
 36. Gimeno-Santos E, Frei A, Steurer-Stey C, et al. Determinants and outcomes of physical activity in patients with COPD: A systematic review. *Thorax*. 2014;69(8):731-739.
 37. Gläser S, Krüger S, Merkel M, Bramlage P, Herth FJF. Chronic Obstructive Pulmonary Disease and Diabetes Mellitus: A systematic review of the literature. *Respiration*. 2015;89(3):253-264.
 38. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2024 Report). *GOLD Respiratory*; 2024.
 39. Incorvaia C, Russo C, Passalacqua G. Effects of pulmonary rehabilitation on exercise capacity in patients with COPD: A number needed to treat study. *Int J Chron Obstruct Pulmon Dis*. 2009;4:315-321.
 40. Kanaley JA, Colberg SR, Corcoran MH, et al. Exercise/physical activity in individuals with type 2 diabetes: A consensus statement from the American College of Sports Medicine. *Med Sci Sports Exerc*. 2022;54(2):353-368.
 41. Kerti M, Balogh Z, Kelemen K, Varga J. The relationship between exercise capacity and different functional markers in pulmonary rehabilitation for COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:717-724.
 42. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;2015(2):CD003793.
 43. McGarvey LP, Magder S, Butler JP. Systemic inflammation, muscle weakness, and metabolic impairment in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2019;199(4):412-421.
 44. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2006;173(12):1390-1413.
 45. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
 46. Paixão C, Rocha V, Brooks D, Marques A. Unsupervised physical activity interventions for people with COPD: A systematic review and meta-analysis. *Pulmonology*. 2024;30(1):53-67.
 47. Paneroni M, Simonelli C, Saleri M, Bertacchini L, Vitacca M, Scalvini S. Muscle strength and functional capacity in patients with COPD and comorbid type 2 diabetes. *Respir Med*. 2017;129:111-117.
 48. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64.
 49. Spruit MA, Burtin C, De Boever P, et al. COPD and exercise: Does it make a difference? *Breathe*. 2016;12(2):e38-e49.
 50. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
 51. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
 52. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: A systematic review and meta-analysis. *JAMA*. 2011;305(17):1790-1799.
 53. Vogiatzis I, Zakynthinos S, Andrianopoulos V. Physiological mechanisms of exercise limitation and pulmonary rehabilitation in COPD. *Eur Respir Rev*. 2012;21(126):324-332.
 54. Cochrane RoB 2 Tool (for RCTs): Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Hernán, M. A., Hopewell, S., Hróbjartsson, A.,
 55. Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., ... Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*, 366, l4898. <https://doi.org/10.1136/bmj.l4898>
 ROBINS-I Tool (for Non-Randomized Studies):

56. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R.,
57. Deeks, J. J., Hróbjartsson, A., Kirkham, J. J., Jüni, P., Loke, Y. K., Pigott, T. D., ... Higgins, J. P.
58. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*, 355, i4919. <https://doi.org/10.1136/bmj.i4919>