Efficacy of interventions to alter measures of fat-free mass in people with COPD: a systematic review and meta-analysis

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Exercise training and nutritional supplementation are not effective in isolation to increase fat-free mass, but show promise when used in combination in people with COPD. Anabolic steroids are efficacious for increasing fat-free mass in people with COPD. https://bit.ly/3A6O2fE

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Abstract

Introduction Low fat-free mass (FFM) is linked to poor health outcomes in COPD, including impaired exercise tolerance and premature death. The aim of this systematic review was to synthesise evidence on the effectiveness of interventions for increasing FFM in COPD.

Methods Searches of electronic databases (MEDLINE, Cochrane Library, Embase, Web of Science, Scopus) and trial registers (ClinicalTrials.gov) were undertaken from inception to August 2022 for randomised studies of interventions assessing measures of FFM in COPD. The primary outcome was change in FFM (including derivatives). Secondary outcomes were adverse events, compliance and attrition.

Results 99 studies (n=5138 people with COPD) of 11 intervention components, used alone or in combination, were included. Exercise training increased mid-thigh cross-sectional area (k=3, standardised mean difference (SMD) 1.04, 95% CI 0.02–2.06; p=0.04), but not FFM (k=4, SMD 0.03, 95% CI −0.18–0.24; p=0.75). Nutritional supplementation significantly increased FFM index (k=11, SMD 0.31, 95% CI 0.13–0.50; p<0.001), but not FFM (k=19, SMD 0.16, 95% CI −0.06–0.39; p=0.16). Combined exercise training and nutritional supplementation increased measures related to FFM in 67% of studies. Anabolic steroids increased FFM (k=4, SMD 0.98, 95% CI 0.24–1.72; p=0.009). Neuromuscular electrical stimulation increased measures related to FFM in 50% of studies. No interventions were more at risk of serious adverse events, low compliance or attrition.

Discussion Exercise training and nutritional supplementation were not effective in isolation to increase FFM, but were for localised muscle and index measures, respectively. Combined, exercise and nutritional supplementation shows promise as a strategy to increase FFM in COPD. Anabolic steroids are efficacious for increasing FFM in COPD.

Introduction

COPD is characterised by a progressive and irreversible decline in lung function [1]. In addition, COPD is recognised as a systemic disease with significant extrapulmonary effects [1]. Loss of skeletal muscle mass is a well described and clinically relevant systemic consequence of COPD. Across the disease severity spectrum of COPD, the prevalence of abnormally low muscle mass (*i.e.* sarcopenia or cachexia) is estimated to be ∼23% [2]. Proposed pathophysiological mechanisms include 1) disease-related factors such as systemic inflammation; 2) ageing; and 3) behaviour modification, particularly less time spent physically active and more time spent sedentary [3, 4].

Importantly, low muscle mass is not just a systemic manifestation affecting people with COPD who are underweight, but also those who are pre-obese or obese, termed sarcopenic obesity, which is similarly associated with poor health outcomes in COPD [3, 5]. People with COPD who possess higher muscle or fat-free mass have a better quality of life [6] and prognosis [7, 8]. In addition, a systematic review from our laboratory recently identified a positive association between muscle or fat-free mass and exercise tolerance in COPD [9]. This has led to low muscle mass being recognised as a treatable trait of COPD to help alleviate disease burden and improve clinical health outcomes [10].

Despite abnormally low muscle mass being a prevalent and clinically meaningful extrapulmonary manifestation of COPD, it is still unclear how to best treat this trait [11]. Current evidence and clinical advice for treating low muscle mass in COPD primarily centres around nutritional supplementation and/or exercise training [12]. However, previous systematic reviews exploring the benefits of nutritional supplementation for increasing fat-free mass in COPD have reported conflicting results, with the evidence base appearing more favourable in people with COPD who are malnourished [13–17]. Likewise, the effects of exercise training on increasing measures related to muscle or fat-free mass in COPD are inconsistent, as reported in two previous systematic reviews [18, 19]. Despite the prominence of nutritional supplementation and exercise training as methods to increase measures of fat-free mass in COPD, which have been the focus of previously discussed reviews, little is known about other interventions and their potential benefit. Therefore, the primary aim of this systematic review and meta-analysis was to collate and synthesise available evidence from randomised studies to estimate the size of the effect of interventions to alter measures of fat-free mass in COPD. The secondary aim was to assess adverse events, compliance and attrition with interventions to alter measures of fat-free mass in COPD.

Methods

The protocol for this review (CRD42020202052) was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO; www.crd.york.ac.uk/PROSPERO/). Protocol deviations are outlined in the supplementary material. This systematic review was reported following Preferred Reporting Items for Systematic reviews and Meta-Analyses reporting guidelines [20].

Population

Adults aged ⩾18 years with either a clinical (*i.e.* by a physician) and/or spirometry-determined (forced expiratory volume in 1 s to forced vital capacity ratio of <0.70 or below the lower limit of normal) diagnosis of COPD.

Intervention

We examined the effect of an intervention on measures related to fat-free mass in COPD. Studies assessing a combination of two or more interventions as adjunctive therapies were also included.

Comparator

Comparator groups of any form were included. Where adjuncts to interventions were assessed, the standalone intervention groups were considered as comparators (*e.g.* nutritional supplementation + exercise training *versus* exercise training). Healthy comparator groups were excluded from this review.

Outcomes

Reported measures of fat-free mass, or derivatives including lean mass, skeletal muscle mass, muscle cross-sectional area, circumference measurements, body cell mass and phase angle, either as a primary or secondary outcome. The primary outcome of this review was measures related to fat-free mass. Secondary outcomes were adverse events, compliance and attrition.

Study design

Randomised studies were included. Studies that used a randomised crossover design were eligible up to the point of crossover. Studies were excluded from this review if they were nonrandomised, observational or cohort studies; narrative or systematic reviews; case studies; editorials; a thesis; or conference abstracts.

Search strategy

The Cochrane Database of Systematic Reviews, PROSPERO and the Database of Abstracts of Reviews of Effects were searched to identify any relevant published or ongoing systematic reviews.

Searches of the following bibliographic databases and trial registers were undertaken: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Web of Science Core Collection, Scopus and Clinicaltrials.gov. Search parameters were set from inception to 19 August 2022 with no limit

on language. Search terms were structured around the population (*e.g.* "COPD") and outcome (*e.g.* "fat-free mass") of interest. The search strategy conducted in MEDLINE is displayed in supplementary table S1 with Medical Subject Headings terms adapted for use in other databases in consultation with a medical librarian. Searches were supplemented with forward and backward citation tracking from included studies and review articles identified from the search process.

Selection process

References identified from the search process were imported into EndNote referencing software (Clarivate Analytics, Philadelphia, PA, USA). After removal of duplicate citations, remaining unique references were exported to Rayyan software (Rayyan Systems, Cambridge, MA, USA) [21] to be independently screened based on title and abstract by two reviewers. Full-text papers were requested for studies not excluded based on title/abstract and independently reviewed by two reviewers for eligibility. Any discrepancies in study inclusion decisions were resolved through discussion and consensus, or by consultation with a third reviewer. Where possible, attempts were made to obtain potentially eligible studies published in a language other than English and translated for screening against eligibility criteria.

Data collection process and data items

Data extraction was completed using an adapted Microsoft Excel form based on the Cochrane data extraction template. This template was piloted on a small subset of studies and subsequently refined. A single reviewer extracted data from eligible studies, which was cross-checked for accuracy by a second reviewer. Data items extracted from each study (supplementary table S2) and further information can be found in the supplementary material.

Risk-of-bias assessment

The revised Cochrane tool for risk of bias [22] was used to evaluate risk of bias. The domains assessed were bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in the measurement of the outcome; and bias in the selection of the reported result. Individual domains were categorised as having high, unclear or low risk of bias. Domain ratings were pooled to provide an overall risk of bias assessment of low (all domains were found to be of low risk of bias), some concerns (some concerns raised in at least one domain in the absence of any domains with a high risk of bias) or high (at least one domain with a high risk of bias, or some concerns across multiple domains). Risk-of-bias assessments were undertaken independently by two reviewers with any disagreements resolved through discussion and consensus or the inclusion of a third reviewer.

Data synthesis strategy

Meta-analyses were performed in accordance with Cochrane guidance using Review Manager version 5.4 (http://revman.cochrane.org/). Measures of effect for continuous outcomes were computed as mean differences or standardised mean differences where appropriate. Post-intervention values were only used when pre-intervention values were deemed sufficiently homogeneous between intervention and comparator groups. Where mean differences were reported without accompanying standard deviation values, attempts were made to impute for these values using approaches deemed suitable by Cochrane guidelines [23], including calculating correlation coefficients derived from other studies included in the same analyses; converting 95% confidence intervals to standard deviations; or using a conservative correlation coefficient of 0.5 according to previous formulae [24]. Risk ratios were used for dichotomous outcomes. Individual study estimates were statistically combined using a generic inverse random-effects method. The I^2 value was used to determine statistical heterogeneity in meta-analyses. Potential sources of heterogeneity in meta-analyses were explored when the I^2 statistic was >40%. Pre-specified subgroup analyses to determine potential sources of heterogeneity according to clinical and methodological factors included population characteristics, intervention characteristics, comparator type and outcome measures. The generalised terms of "depleted" or "nondepleted" were adopted for population characteristics in studies that recruited or subgrouped participants based on body composition characteristics; however, no consistent criteria were used to define participants as depleted due to the varying definitions adopted across studies. All individual study definitions of depleted are defined in the footnotes of supplementary table S3. A minimum of three studies were required to perform a meta-analysis. Sensitivity analyses were planned based on studies with a low risk of bias, but as no meta-analyses of primary outcomes presented with three or more studies with a low risk of bias, these analyses were not undertaken. Studies unable to be included in meta-analyses were narratively synthesised. Further details surrounding the data synthesis strategy can be found in the supplementary material.

Results

Following removal of duplicates, the search strategy identified 14 164 records to be screened, of which 13 097 were excluded based on title and abstract. Full texts were obtained for the remaining 1067 records, of which 99 met the inclusion criteria with nine of these being studies utilising the same dataset of an included study, leaving a total of 90 included studies (figure 1).

Characteristics of included studies

The 90 included studies were published between 1987 and 2022 [25–114] (supplementary table S3). 5138 people with COPD were randomised, with study sample sizes ranging from 14 to 233. The severity of COPD ranged from mild to very severe. Intervention components assessed in studies included nutritional supplementation (*k*=45), exercise training (*k*=45), anabolic steroids (*k*=7), neuromuscular electrical stimulation (*k*=7), inspiratory muscle training (*k*=5), hormone therapy (*k*=4), angiotensin-converting enzyme (ACE)-inhibitors (*k*=2), antibody therapy (*k*=1), lung volume reduction surgery (*k*=1), acupuncture (*k*=1) and behaviour change (*k*=1), with some interventions assessed in combination. Comparator groups varied and included usual care, placebo, sham, different modalities and dosages of exercise training, nutritional supplementation and anabolic steroids, with some comparators utilised as a combination. Interventions varied widely in terms of duration, ranging from 5 days to 24 months. Outcomes of fat-free mass, which were measured in a variety of ways and sometimes utilising multiple tools within single studies, included bioelectrical impedance analysis (n=37), dual-energy X-ray absorptiometry (n=24), tape measure (n=18), muscle biopsy (n=8), computed tomography scan (n=5), ultrasound (n=4), deuterium and bromide (n=4) and magnetic resonance imaging (n=3); measurement tool was not reported in five studies.

High risk of bias was present in 53 (59%) studies; some concerns around bias were apparent in 30 (33%) studies; with low risk of bias present in seven (8%) studies. Elements of risk of bias were mainly apparent due to poor study reporting of randomisation procedures, missing data and a lack of blinding of participants and outcome assessors (supplementary table S4).

Meta-analyses and qualitative synthesis

Exercise training *versus* nonexercise-based care

10 studies [25–32, 92, 115] explored exercise training *versus* nonexercise-based care and assessed 12 different outcomes. The frequency of exercise training ranged from twice daily to twice a week. Training intensity ranged from 50–80% of one repetition maximum/40–80% work rate maximum or was determined by Borg score or baseline measures. Training duration ranged from 30 to 120 min per session with intervention duration ranging from 5 days to 2 years. Training modality was aerobic and/or resistance exercise.

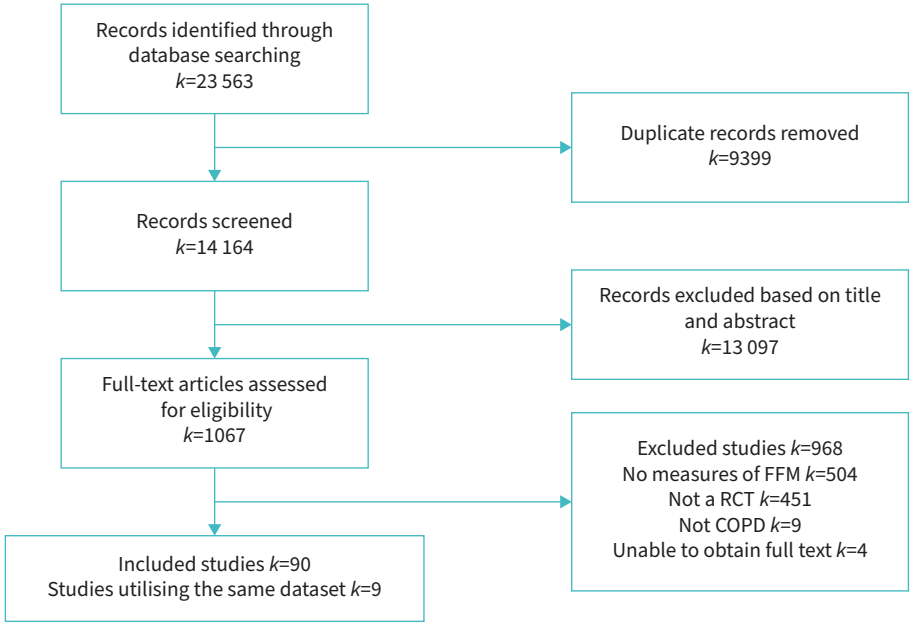


FIGURE 1 Flow diagram of study selection. FFM: fat-free mass; RCT: randomised controlled study.

Meta-analysis of four studies [27, 32, 33, 92] found that exercise training alone did not significantly increase fat-free mass measures compared to nonexercise-based care, with heterogeneity deemed unimportant (standardised mean difference (SMD) 0.03, 95% CI −0.18–0.24, p=0.75; I^2=0%; figure 2a).

Meta-analysis of three studies [25, 29, 31] found that exercise training alone significantly increased measures of mid-thigh cross-sectional area compared to nonexercise-based care, with substantial heterogeneity present (SMD 1.04, 95% CI −0.02–2.06, p=0.04; I^2=68%; figure 2b). Due to the small number of included studies, subgroup analyses were not performed to investigate sources of heterogeneity.

All reported outcomes have been narratively summarised in supplementary table S5. Of the included studies, three (30%) out of 10 [25, 28, 31] reported significant increases in measures related to fat-free mass, with significant outcomes being measures of lower-limb fat-free mass. Alcazar *et al.* [25] reported significant increases in vastus lateralis thickness and mid-thigh cross-sectional area with a combination of aerobic and resistance high-intensity interval exercise *versus* usual care. Farias *et al.* [28] reported significant increases in skeletal muscle mass of the lower limbs with aerobic exercise *versus* usual care. Kongsgaard *et al.* [31] reported significant increases in mid-thigh cross-sectional area with lower-limb resistance exercise *versus* usual care.

Secondary outcomes are reported in the supplementary material and supplementary figure S1.

Nutritional supplementation *versus* no supplementation

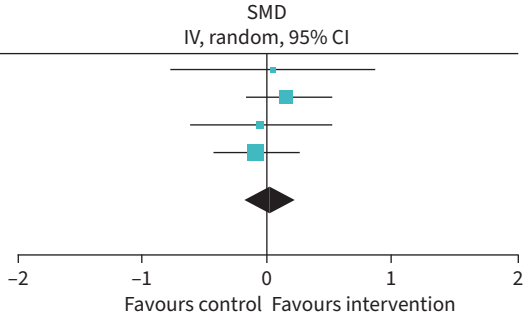
36 studies [44–47, 54–79, 81–84, 103, 114] assessed nutritional supplementation *versus* no supplementation using 24 different outcomes. The supplements included macronutrients; essential, nonessential or branched-chain amino acids; antioxidants; L-carnitine; polyunsaturated fatty acids; herbal remedies; creatine; probiotics; and nitrate. Intervention duration ranged from 9 days to 12 months.

Meta-analysis of 19 studies [44–47, 55, 58–62, 64, 65, 67, 68, 77, 79, 81–83] found that nutritional supplementation alone did not increase fat-free mass measures *versus* no supplementation, with substantial heterogeneity present (SMD 0.16, 95% CI −0.06–0.39, p=0.16; I^2=63%; figure 3a). There was no

a)

Study or subgroup	SMD±SE	Weight	SMD IV, random, 95% CI
Casaburi 2004	0.0526±0.4175	6.6%	0.05 (−0.77–0.87)
Effing 2011	0.1738±0.1712	39.0%	0.17 (−0.16–0.51)
Seymour 2010	−0.0396±0.2863	13.9%	−0.04 (−0.60–0.52)
van Wetering 2010	−0.0777±0.1679	40.5%	−0.08 (−0.41–0.25)
Total (95% CI)		100%	0.03 (−0.18–0.24)

Heterogeneity: τ^2=0.00; Chi^2=1.18, df=3 (p=0.76), I^2=0%
Test for overall effect: Z=0.32 (p=0.75)



b)

Study or subgroup	SMD±SE	Weight	SMD IV, random, 95% CI
Alcazar 2019	2.5822±0.8231	22.3%	2.58 (0.97–4.20)
Gurgun 2013	0.3534±0.3626	40.8%	0.35 (−0.36–1.06)
Kongsgaard 2004	0.8654±0.4497	36.9%	0.87 (−0.02–1.75)
Total (95% CI)		100%	1.04 (0.02–2.06)

Heterogeneity: τ^2=0.53; Chi^2=6.21, df=2 (p=0.04), I^2=68%
Test for overall effect: Z=2.01 (p=0.04)

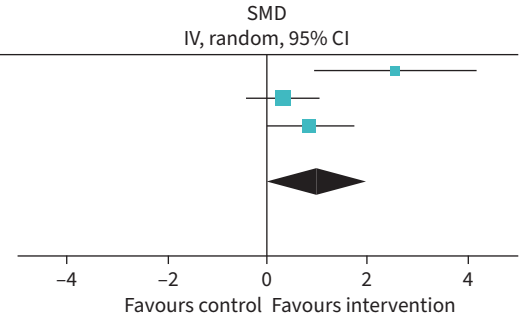
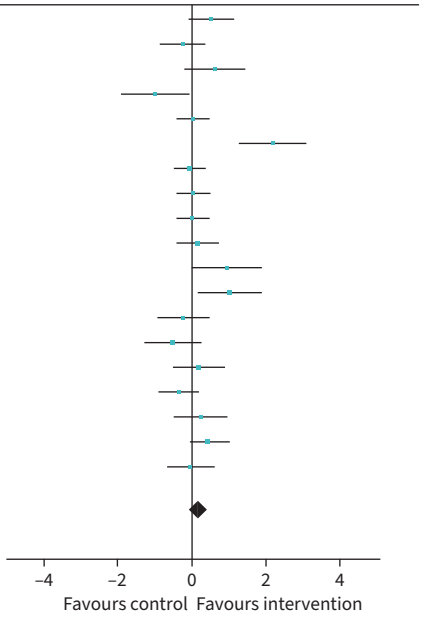


FIGURE 2 Study-level data, effect estimates and forest plot of comparison for change in a) fat-free mass measures and b) measures of mid-thigh cross-sectional area following an exercise training intervention *versus* nonexercise-based care. SMD: standardised mean difference; IV: inverse variance.

a)

Study or subgroup	SMD±SE	Weight	SMD IV, random, 95% CI
Ahmadi 2020	0.5321±0.3076	5.5%	0.53 (−0.07–1.13)
Aldhahir 2021	−0.2467±0.3028	5.5%	−0.25 (−0.84–0.35)
Baldi 2010	0.6313±0.4036	4.3%	0.63 (−0.16–1.42)
Beijers 2020	−0.9738±0.4677	3.6%	−0.97 (−1.89–−0.06)
Broekhuizen 2005	0.0461±0.2239	6.7%	0.05 (−0.39–0.48)
Dal Negro 2010	2.193±0.459	3.7%	2.19 (1.29–3.09)
Dal Negro 2012	−0.0521±0.2132	6.8%	−0.05 (−0.47–0.37)
Deacon 2008	0.0372±0.2239	6.7%	0.04 (−0.40–0.48)
De Benedetto 2018	0.0225±0.2108	6.9%	0.02 (−0.39–0.44)
De Bisschop 2021	0.1545±0.2842	5.8%	0.15 (−0.40–0.71)
Engelen 2022	0.9358±0.4767	3.6%	0.94 (0.00–1.87)
Fuld 2005	1.0278±0.4329	4.0%	1.03 (0.18–1.88)
Hamada 2018	−0.2399±0.351	4.9%	−0.24 (−0.93–0.45)
Ingadottir 2019	−0.5086±0.3751	4.6%	−0.51 (−1.24–0.23)
Pirabbasi 2016	0.1742±0.3503	4.9%	0.17 (−0.51–0.86)
Steiner 2003	−0.3525±0.264	6.1%	−0.35 (−0.87–0.16)
Sugawara 2012	0.2212±0.3622	4.8%	0.22 (−0.49–0.93)
van de Bool 2017	0.461±0.26	6.1%	0.46 (−0.05–0.97)
Vermeeren 2004	−0.037±0.3051	5.5%	−0.04 (−0.63–0.56)
Total (95% CI)		100%	0.16 (−0.06–0.39)

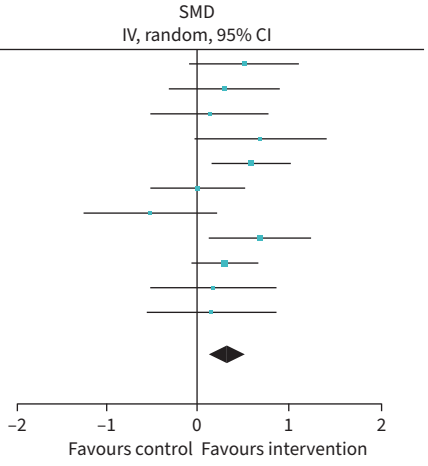
Heterogeneity: τ^2=0.15; Chi^2=48.32, df=18 (p=0.0001), I^2=63%
Test for overall effect: Z=1.41 (p=0.16)



b)

Study or subgroup	SMD±SE	Weight	SMD IV, random, 95% CI
Ahmadi 2020	0.5116±0.3072	8.1%	0.51 (−0.09–1.11)
Aldhahir 2021	0.2959±0.3033	8.3%	0.30 (−0.30–0.89)
Calder 2018	0.1335±0.3248	7.3%	0.13 (−0.50–0.77)
Dal Negro 2010	0.6899±0.3653	6.0%	0.69 (−0.03–1.41)
Dal Negro 2012	0.5957±0.2181	14.1%	0.60 (0.17–1.02)
Gouzi 2019	0±0.2659	10.3%	0.00 (−0.52–0.52)
Ingadottir 2019	−0.5151±0.3753	5.7%	−0.52 (−1.25–0.22)
Marinari 2013	0.6867±0.2792	9.5%	0.69 (0.14–1.23)
Pavitt 2020	0.3039±0.1825	18.3%	0.30 (−0.05–0.66)
Pirabbasi 2016	0.1713±0.3503	6.4%	0.17 (−0.52–0.86)
Sugawara 2012	0.1544±0.3615	6.1%	0.15 (−0.55–0.86)
Total (95% CI)		100%	0.31 (0.13–0.50)

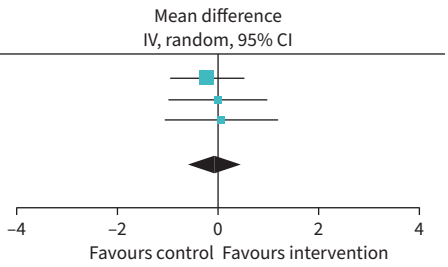
Heterogeneity: τ^2=0.02; Chi^2=11.87, df=10 (p=0.29), I^2=16%
Test for overall effect: Z=3.32 (p=0.0009)



c)

Study or subgroup	Mean difference±SE	Weight	Mean difference IV, random, 95% CI
Ahmadi 2020	−0.21±0.3708	50.8%	−0.21 (−0.94–0.52)
Borghi-Silva 2006	0±0.5	27.9%	0.00 (−0.98–0.98)
Khan 2016	0.09±0.5727	21.3%	0.09 (−1.03–1.21)
Total (95% CI)		100%	−0.09 (−0.61–0.43)

Heterogeneity: τ^2=0.00; Chi^2=0.24, df=2 (p=0.89), I^2=0%
Test for overall effect: Z=0.33 (p=0.74)



d)

Study or subgroup	Mean difference±SE	Weight	Mean difference IV, random, 95% CI
Borghi-Silva 2006	0±1.4577	13.8%	0.00 (−2.86–2.86)
Knowles 1988	1.6±1.2712	18.2%	1.60 (−0.89–4.09)
Lambert 1998	1.5±0.8485	40.8%	1.50 (−0.16–3.16)
Lewis 1987	−0.3±1.038	27.2%	−0.30 (−2.33–1.73)
Total (95% CI)		100%	0.82 (−0.24–1.88)

Heterogeneity: τ^2=0.00; Chi^2=2.50, df=3 (p=0.48), I^2=0%
Test for overall effect: Z=1.51 (p=0.13)

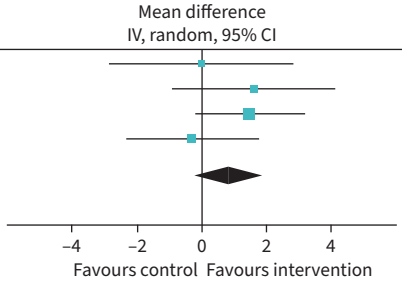


FIGURE 3 Study-level data, effect estimates and forest plot of comparison for change in a) fat-free mass measures, b) fat-free mass index measures, c) arm circumference and d) arm muscle circumference following nutritional supplementation *versus* no supplementation. SMD: standardised mean difference; IV: inverse variance.

evidence of publication bias (supplementary figure S2A). Subgroup analyses performed to investigate heterogeneity found no statistically significant differences between subgroups (all, p⩾0.05) (supplementary figure S2B–E).

Meta-analysis of 11 studies [44, 45, 56, 58, 59, 66, 68, 75–77, 81] found that nutritional supplementation alone significantly increased fat-free mass index *versus* no supplementation, with heterogeneity deemed unimportant (SMD 0.31, 95% CI 0.13–0.50, p<0.001; I^2=16%; figure 3b). There was no evidence of publication bias (supplementary figure S3).

Meta-analysis of three studies [44, 54, 70] found that nutritional supplementation alone did not increase arm circumference *versus* no supplementation, with heterogeneity deemed unimportant (mean difference (MD) −0.09 cm, 95% CI −0.61–0.43 cm, p=0.74; I^2=0%; figure 3c).

Meta-analysis of four studies [54, 71, 72, 74] found that nutritional supplementation alone did not increase arm muscle circumference *versus* no supplementation, with heterogeneity deemed unimportant (MD 0.82 cm, 95% CI −0.24–1.88 cm, p=0.13; I^2=0%; figure 3d).

All reported outcomes have been summarised narratively in supplementary table S6. Of the included studies, four (11%) out of 36 [44, 64, 65, 75] studies reported significant increases in fat-free mass measures with nutritional supplementation alone *versus* no supplementation. Fuld *et al.* [65] reported significant increases in fat-free mass with creatine supplementation *versus* placebo. Likewise, Marinari *et al.* [75] reported significant increases in fat-free mass index with a combination of coenzyme Q-TER and creatine supplementation *versus* placebo. Ahmadi *et al.* [44] reported significant increases in fat-free mass and fat-free mass index with whey protein (15.9 $g \cdot day^{-1}$) fortified with magnesium and vitamin C supplementation *versus* usual care. Engelen *et al.* [64] reported significant increases in whole-body lean mass and lean mass of the extremities with polyunsaturated fatty acid supplementation *versus* placebo. Two studies [47, 59] reported significant decreases in fat-free mass measures with nutritional supplementation *versus* no supplementation. Beijers *et al.* [47] reported significant decreases in fat-free mass, lean mass, leg lean mass and trunk lean mass with resveratrol supplementation *versus* placebo. Dal Negro *et al.* [59] reported significant decreases in fat-free mass with essential amino acid supplementation *versus* placebo.

Secondary outcomes are reported in the supplementary material and supplementary figure S4.

Anabolic steroids versus *placebo*

Seven studies [92, 93, 101–104, 106] assessed anabolic steroids (specifically testosterone enanthate or nandrolone decanoate) *versus* placebo on nine different outcomes. Intervention duration ranged from 6 to 27 weeks.

Meta-analysis of five studies [92, 93, 102, 104, 106] found that anabolic steroids significantly increased fat-free mass measures *versus* placebo, with substantial heterogeneity present (SMD 0.98, 95% CI 0.24–1.72, p<0.001; I^2=71%; figure 4). Subgroup analyses found a significantly greater increase in fat-free mass measures (p=0.01) in depleted people with COPD (SMD 2.68, 95% CI 1.27–4.08, p<0.001) as opposed to nondepleted individuals (SMD 0.68, 95% CI 0.09–1.27, p=0.02; supplementary figure S5B). No subgroup differences were found for measurement tool (p=0.13; supplementary figure S5A) or intervention type (p=0.10; supplementary figure S5C). Study designs were not homogeneous enough to permit a subgroup analysis.

All reported outcomes have been summarised narratively in supplementary table S7. Four (57%) [92, 93, 102, 106] of the seven included studies reported significant increases in fat-free mass measures with anabolic steroids *versus* placebo. These four studies [92, 93, 102, 106] all reported significant increases in either fat-free or lean mass. In addition, Ferreira *et al.* [102] reported significant increases in thigh and mid-arm muscle circumference with anabolic steroids. Casaburi *et al.* [92] reported significant increases in leg and arm lean mass with anabolic steroids.

Secondary outcomes are reported in the supplementary material and supplementary figure S6.

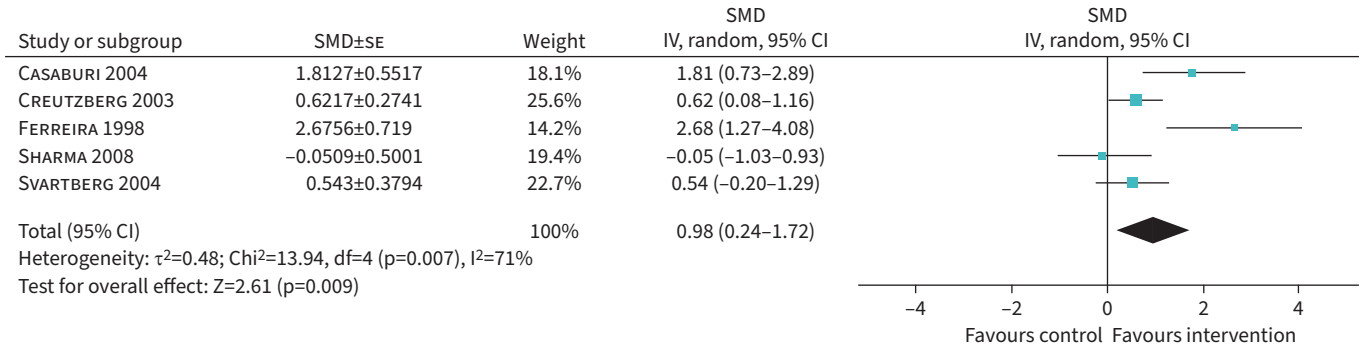


FIGURE 4 Study-level data, effect estimates and forest plot of comparison for change in fat-free mass measures following anabolic steroid supplementation *versus* placebo. SMD: standardised mean difference; IV: inverse variance.

Other interventions/comparisons

Other interventions or comparisons that it was not possible to meta-analyse due to a lack of studies or lack of availability of appropriately formatted data included exercise training of different modalities (*e.g.* resistance *versus* aerobic, eccentric *versus* concentric, single-limb *versus* two-limb); nutritional supplementation combined with exercise training; hormonal therapy; neuromuscular electrical stimulation; ACE-inhibitors; inspiratory muscle training; antibody therapy; lung volume reduction surgery; acupuncture; behaviour change; and anabolic steroids combined with exercise training or nutritional supplementation. The results of these interventions/comparisons have been summarised narratively in the supplementary material and in supplementary table S8.

Discussion

This is the first systematic review to synthesise evidence from randomised studies exploring the efficacy of interventions, of any nature, for increasing measures related to fat-free mass in people with COPD. The main findings were 1) an extensive array of interventions have been explored for their effect on fat-free mass in people with COPD, which vary in their type and dose, making it difficult to ascertain what might be the optimal interventional approach; 2) there is currently limited evidence that exercise training or nutritional supplementation alone are sufficient to improve measures of fat-free mass, but nutritional supplementation appears to be efficacious for increasing index measures of fat-free mass; 3) combining aerobic and resistance exercise training with nutritional supplementation may be more effective than either intervention alone to increase fat-free mass; 4) anabolic steroids are effective for increasing measures of fat-free mass, particularly in people with COPD classified as depleted; and 5) alternative approaches such as neuromuscular electrical stimulation have shown promise for increasing lower limb muscle mass.

The findings of the current review, that exercise training alone was not sufficient to increase measures of fat-free mass in COPD, are somewhat surprising given the established evidence base in healthy populations showing that exercise training, specifically resistance-based exercise training, increases skeletal muscle mass [116]. A previous review in the COPD population supported the benefits of exercise training on increasing fat-free mass, although the review in question was narrative in nature and included nonrandomised studies [18], whereas the current review pooled randomised studies only. Assessment of study characteristics may explain, at least in part, the lack of observed effect in terms of increases in measures of fat-free mass. Alcazar *et al*. [25] and Kongsgaard *et al*. [31] were two of only three studies to demonstrate a significant increase in measures of fat-free mass with exercise training. Notably, these studies were well designed to induce muscle hypertrophy given that they focussed heavily on resistance exercise training and worked in line with the progressive overload principle as well as the intensity framework outlined by the American College of Sports Medicine, which recommends one to three sets of eight to 12 repetitions at an intensity of 70–85% of one repetition maximum [117]. Such information about exercise training is often poorly reported or assessed in studies surrounding people with COPD. The three studies reporting significant improvements in measures of fat-free mass ranged from 8 to 12 weeks in duration, with the remaining studies ranging from 5 days to 24 months. Therefore, it would appear that intensity and progressive overload are more important factors than duration when it comes to inducing muscle hypertrophy in COPD with exercise training. However, we cannot discount the possibility that another factor contributing to this lack of observed effect with measures of fat-free mass may be the heterogeneous response to exercise experienced by people within the COPD population, whereby some subgroups are recognised as nonresponders [118]. It could be speculated that anabolic resistance, which is

present in people with COPD [119], could play a role in these nonresponders. However, recent evidence has suggested that impaired responses to resistance exercise training do not appear to be apparent in COPD [120]. It is important to acknowledge that positive effects were seen with mid-thigh cross-sectional area. Assessing studies included in this meta-analysis suggested that exercise and outcomes tailored to specific muscle groups, in this case the lower-limbs, are required to observe changes in measures related to fat-free mass. The beneficial effects of training specific muscle groups are likely to be diluted if utilising whole-body fat-free mass measures as opposed to localised measures.

In line with the findings of the current review, two prior reviews reported a lack of effect of nutritional supplementation on fat-free mass measures in COPD [13, 14]. The variation in findings between studies included in this review may in part be explained by study design. As outlined in supplementary table S3, very few studies included in our review tailored nutritional supplementation regimens to individual patient needs by accounting for their energy expenditure requirements and recommended daily allowances, with most studies applying a "one size fits all" approach, aiming to solely increase calorie intake, but not standardising this across people involved within the study. This is critically important, as depleted people with COPD require a larger increase in calorie intake than nondepleted people, who may not require supplementation at all. Many different types of supplementation were implemented among the studies included in our review. It could be argued that some supplements, mainly resveratrol (an antioxidant), are not designed to increase fat-free mass measures; hence the negative results observed in the single study that assessed this [47]. With normative ageing, it is well established that anabolic resistance occurs [121]. In COPD, anabolic resistance may also be present [119], meaning that higher amounts of protein may be required as part of nutritional supplementation to overcome this barrier. However, there is evidence to suggest that there is no disease-specific heightening of anabolic resistance in COPD compared to healthy aged adults [57, 122], meaning that dietary protein requirements are probably similar between these two groups. The majority of included studies implementing protein supplementation did so at a dosage of $<20\ g \cdot day^{-1}$. It has been demonstrated that older adults are less sensitive to 20 g protein ingestion following exercise *via* attenuated muscle protein synthesis and may require greater dosages, up to $40\ g \cdot day^{-1}$ [123]. The relatively low daily dose of protein used in most included studies may help explain the lack of observed effects in the current review. In addition to this, only two studies [46, 78] provided targeted protein supplementation on a gram-per-kilogram of body mass basis, but neither of these studies reported significant increases in fat-free mass measures. Additionally, very few studies assessed or utilised assessments of protein intake prior to commencing protein supplementation to determine whether people were meeting their recommended daily allowance. This is important as it details whether supplementation was targeted to enable people with COPD to meet the recommended daily allowance for protein, or whether the target was to exceed the recommended daily allowance. Even though most studies supplemented their COPD participants with more protein than otherwise provided by their normal diet, it still may not have been enough to optimise muscle protein synthesis and hypertrophy.

Conventionally, it is seen that nutritional supplementation and resistance exercise training are required to increase measures of fat-free mass [124]. Two out of three studies included in our review reported significant increases in measures of fat-free mass when these two interventions were used in combination, which is promising and deserves greater attention. Nutritional supplementation and resistance training work well together, as resistance exercise can increase the rate of muscle protein synthesis while concurrently, nutritional supplementation, particularly dietary protein supplementation, can suppress muscle protein breakdown, providing an ideal environment to support muscle growth [124].

Our findings relating to increasing fat-free mass measures with anabolic steroids (specifically testosterone enanthate and nandrolone decanoate) in COPD support the results of studies in healthy adults [125] and people with diseases such as chronic renal failure, muscular dystrophy and HIV [126], as well as recent evidence in people with COPD [127, 128]. Substantial heterogeneity was observed in our findings, suggesting a wide range of effects. Subgroup analyses suggested that people with COPD variably classified as depleted (*e.g.* malnourished, underweight, sarcopenic) are more likely to benefit from anabolic steroids than their nondepleted counterparts. However, this subgroup effect was driven primarily by the results of a single study by Ferreira *et al*. [102], which was different to other included studies. Most notably, it was the only study to supplement a baseline 250 mg dose of intramuscular testosterone with a daily 12 mg dose of oral stanozolol (testosterone) as opposed to periodic top-ups (*i.e.* every 1–4 weeks). Ferreira *et al*. [102] had the longest intervention period of 27 weeks, with Svartberg *et al*. [106] providing a 250 mg dose of testosterone enanthate every 4 weeks for 26 weeks, which also produced significant increases in fat-free mass in a nondepleted population. Other included studies in nondepleted groups of people with COPD were of a shorter duration (6–16 weeks) and utilised either testosterone enanthate ($100\ mg \cdot week^{-1}$) or nandrolone decanoate (25 mg and 50 mg every 2 weeks for females and males, respectively). This

suggests that in people with COPD (especially those who are depleted), daily doses of anabolic steroids over an extensive period (*i.e.* ⩾6 months) may be needed to optimise their interventional efficacy in terms of increasing fat-free mass measures.

Half of the six studies that assessed neuromuscular electrical stimulation as a therapy reported increases in measures of fat-free mass. These findings are of interest, as neuromuscular electrical stimulation is often used to target muscle strength. Neuromuscular electrical stimulation has also been shown to preserve muscle mass during periods of immobilisation in healthy adults [129], but it has been noted that such changes in muscle mass require further investigation [130]. While all included studies in the current review were assessed in groups of nondepleted and nonhospitalised people with COPD, neuromuscular electrical stimulation shows promise for increasing localised (*i.e.* quadriceps or calf) fat-free mass measures as opposed to focusing on preserving fat-free mass measures in people that are hospitalised/bed-bound. In addition to this, previous research in healthy adults and rats has shown that neuromuscular electrical stimulation in isolation may not be sufficient to induce muscle hypertrophy, but is efficacious when used in combination with blood flow restriction [131–134]. This combination is an unexplored avenue in people with COPD that should be addressed.

Given the lack of studies assessing growth hormones, bimagrumab, acupuncture, lung volume reduction surgery, ACE-inhibitors and behaviour change, it is difficult to draw meaningful interpretations about their efficacy or lack thereof at this stage. However, for certain interventions such as acupuncture, lung volume reduction surgery, ACE-inhibitors and behaviour change (depending on whether behaviour change specifically targets resistance exercise training and nutrition), there is little to no physiological rationale for a direct effect on muscle hypertrophy. Thus, such interventions should not be used in people with COPD for the sole purpose of increasing measures of fat-free mass. In contrast, there is a physiological rationale for using growth hormones [135] and bimagrumab [136] to promote muscle anabolism, and these interventions deserve further attention in COPD.

Methodological considerations

A strength of the current review is that successful efforts were made to obtain data from several study authors to permit the inclusion of more studies in meta-analyses. However, this was not the case in all studies and the exclusion of studies from certain analyses should be considered a limitation, even though these were included narratively to provide balance. Some analyses, for example nutritional supplementation *versus* no supplementation, presented with substantial heterogeneity that could not always be explained by subgroup analyses; thus, for certain outcomes it is not clear where the "true" effect lies. The varying definitions used by studies in the current review for conditions such as cachexia, sarcopenia, malnourished and others, grouped together under the umbrella term "depleted", are likely to have impacted the findings of our subgroup analyses. The deviations from the original pre-registered protocol, as outlined in the supplementary material, should also be considered a limitation of this review. It is important to note that we focused on measures of fat-free mass alone and did not consider other indices of muscle dysfunction common in COPD, specifically strength and endurance. While there is a positive correlation between whole-body lean mass and each of quadriceps muscle strength and endurance in COPD [137], changes in measures of fat-free mass do not always translate to increases in muscle strength and/or endurance [42, 87, 138]. Therefore, making assumptions with regards to changes in muscle strength and/or endurance based on changes in fat-free mass measures presented in the current review should be done with caution. It is important to highlight that many of the studies included in the current review only included males with COPD. In particular, only two out of seven studies involving anabolic steroids included females. Given the sexual dimorphism that reportedly exists in, for example, the physiological response to aerobic and resistance exercise training [139, 140], addressing the biological sex knowledge gap by including females in therapeutic trials focused on muscle hypertrophy in COPD should be a top priority in moving forward. While our comprehensive and broad review brings together evidence on interventions to alter fat-free mass measures in COPD, it is important to highlight that not all included studies were specifically designed to increase measures of fat-free mass (*i.e.* fat-free mass was not the primary outcome and studies may have been underpowered to demonstrate interventional efficacy on fat-free mass). Finally, the lack of reporting of between-group differences for some narratively synthesised studies means that the effects observed in those studies cannot be fully compared with other included studies.

Implications for clinical practice

Given the mixed findings between outcomes for exercise training and nutritional supplementation, questions remain about utilising these interventions in isolation to increase measures of fat-free mass in COPD. Exercise training is effective at inducing muscle hypertrophy when properly prescribed in terms of frequency, intensity, time and type (*i.e.* mainly resistance-based) [116], and even more so when combined

with nutritional supplementation (*i.e.* protein and creatine) [124, 141] on an individualised basis in healthy adults. Assessing the characteristics of the studies included in our review, it is likely that exercise training-based interventions were not optimised to increase measures of fat-free mass in COPD. Narrative synthesis suggests more therapeutic promise of utilising exercise training and nutritional supplementation in combination for increasing measures of fat-free mass in COPD. While increases in fat-free mass measures were demonstrated with anabolic steroids, substantial heterogeneity was present, but suggested this treatment modality would be more beneficial for people with COPD who are depleted. The number of studies assessing anabolic steroids was relatively small to warrant recommendations for clinical practice. Research is regularly published assessing interventions to increase measures of fat-free mass in COPD, especially with the identification of sarcopenia (abnormally low skeletal muscle mass) as a treatable trait of COPD [10], paving the way for regular updates on interventions specifically highlighted within the current review. In the meantime, clinicians should follow consensus/expert-based guidance for exercise training and nutritional supplementation [142, 143].

Implications for future research

The utilisation of a wide variety of outcomes for assessing fat-free mass related measures is an area for consideration in future research. A consensus driven approach to developing a core set of outcomes for body composition measurement (*e.g.* fat-free mass, lean mass, skeletal muscle mass) that accounts for the availability of equipment (*e.g.* bioelectrical impedance analysis, dual-energy X-ray absorptiometry) should be considered. Furthermore, the choice and availability of outcomes should be carefully considered to increase specificity, as well as sensitivity, with the intended intervention. For example, segmental measures of fat-free mass may be better suited to interventions targeting specific limbs (*i.e.* lower-limb resistance exercise training), as opposed to whole-body measures which may dilute the signal. Importantly, future studies should tailor interventions to each individual with COPD instead of adopting a "one size fits all" approach. This includes prescribing mainly resistance exercise training to a moderate–high intensity with progressive overload and conducting regular re-evaluations of strength to ensure adequate progression of intensity. In addition, nutritional supplementation should be provided, mainly in the form of a high protein diet, which is dosed to the requirement(s) of the population. In practice, this is likely to be targeting people with COPD who are depleted, as this group has been identified as being more amenable to interventions targeted at increasing muscle mass [142]. With this in mind, research examining subgroups such as sarcopenia within recruited populations should be considered, making sure to define these populations based on the definitions provided by expert-based panels such as the European Working Group on Sarcopenia in Older People [144]. Given the promising findings surrounding the combination of exercise and nutritional supplementation, future research should look to assess the efficacy of multiple interventions in tandem (*e.g.* resistance exercise training + protein supplementation + anabolic steroids) with a specific view of targeting people with COPD who are cachectic or sarcopenic. Research should also make sure that appropriate statistical analyses are undertaken to permit comparison of between-group differences, instead of solely analysing within-group comparisons which fail to provide an observation of the interaction effect between intervention and comparator groups. Randomised studies should also be designed with the Cochrane risk-of-bias tool (version 2) in mind to promote more high-quality randomised controlled studies. Finally, the lack of assessment of compliance with interventions is an area that should be considered given the clinical importance of adherence for intervention implementation and efficacy.

Conclusions

The results of this systematic review and meta-analysis suggest that exercise training increases localised fat-free mass measures (*e.g.* mid-thigh cross-sectional area), but not whole-body fat-free mass measures; and nutritional supplementation increases index measures of fat-free mass. Anabolic steroids were shown to be effective at increasing measures related to fat-free mass in people with COPD. Narrative analyses supported the efficacy of nutritional supplementation and exercise training in combination for increasing measures related to fat-free mass in COPD. Future research should assess combinations of interventions and be sure to tailor interventions in an individualised manner to target increases in fat-free mass in accordance with established guidelines for prescription (*i.e.* resistance training in accordance with frequency, intensity, time and type as well as progressive overload principles, and setting nutritional supplementation targets based on recommended daily allowances to optimise muscle hypertrophy).

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