Content

Supplementary material for *Effects of nutritional interventions in individuals with chronic obstructive lung disease: A systematic review of randomized controlled trials*

Text S1: Detailed search string in Embase

Database: Embase <1974 to 2021 August 31>
Search Strategy: ----------

1. 1 exp chronic obstructive lung disease/ (135754)
2. 2 ("Chronic Obstructive Pulmonary Disease" or COPD or COAD or Chronic Obstructive Airway Disease or Chronic Obstructive Lung Disease or

Chronic Airflow Obstructions or Chronic Airflow Obstruction).ti,ab,kw. (119346)

3. 3 1 or 2 (161837)
4. 4 exp diet therapy/ (349044)
5. 5 exp nutrition/ (2200000)
6. 6 exp food/ (1031087)
7. 7 exp diet/ (326727)
8. 8 (Diet or Nutrition* or Food or Vegetable* or Fruit* or Nut or Nuts or Protein* or Amino Acid* or Fatty acid* or Micronutrient* or

Phytochem* or Vitamin* or Minerals* or Antioxidant* or Carbohydrate*).ti,ab,kw. (5510940)

9. 9 4or5or6or7or8(6630190)
10. 10 ((respirator* or lung) and (inflammation or immune)).ti,ab,kw. (138796)
11. 11 respiratory function.ti,ab,kw. (16960)
12. 12 improved lung function.ti,ab,kw. (1328)
13. 13 exacerbat*.ti,ab,kw. (166442)
14. 14 10 or 11 or 12 or 13 (312766)
15. 15 3 and 9 and 14 (6134)
16. 16 limit 15 to "therapy (best balance of sensitivity and specificity)" (667)
17. 17 limit 15 to "therapy (maximizes sensitivity)" (1303)
18. 18 limit 15 to "therapy (maximizes specificity)" (240)

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Supplementary material for *Effects of nutritional interventions in individuals with chronic obstructive lung disease: A systematic review of randomized controlled trials*

Text S2: Detailed search string in Medline and Cochrane

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to August 31, 2021> Search Strategy:
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1. 1 exacerbat*.ti,ab,kw. (108473)
2. 2 improved lung function.ti,ab,kw. (693)
3. 3 respiratory function.ti,ab,kw. (11617)
4. 4 ((respirator* or lung) and (inflammation or immune)).ti,ab,kw. (84787)
5. 5 1or2or3or4(199873)
6. 6 (Chronic Obstructive Pulmonary Disease or COPD or COAD or Chronic Obstructive Airway Disease or Chronic Obstructive Lung Disease or

Chronic Airflow Obstructions or Chronic Airflow Obstruction).ti,ab,kw. (67677)

7. 7 exp Pulmonary Disease, Chronic Obstructive/ (56161)
8. 8 6 or 7 (88195)
9. 9 (Diet or Nutrition* or Food or Vegetable* or Fruit* or Nut or Nuts or Protein* or Amino Acid* or Fatty acid* or Micronutrient* or

Phytochem* or Vitamin* or Minerals* or Antioxidant* or Carbohydrate*).ti,ab,kw. (4585273)

10. 10 exp Diet Therapy/ (54812)
11. 11 Nutrition Therapy/ (2427)
12. 12 exp "Diet, Food, and Nutrition"/ (1719790)
13. 13 9 or 10 or 11 or 12 (5500225)
14. 14 5 and 8 and 13 (3052)
15. 15 limit 14 to "therapy (best balance of sensitivity and specificity)" (216)
16. 16 limit 14 to "therapy (maximizes specificity)" (123)
17. 17 limit 14 to "therapy (maximizes sensitivity)" (1220)

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Text S3: Additional search in Embase

Database: Embase <1974 to 2021 August 26>
Search Strategy:
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1 exp chronic obstructive lung disease/ (146587)
2 ("Chronic Obstructive Pulmonary Disease" or COPD or COAD or Chronic Obstructive Airway Disease or Chronic Obstructive Lung Disease or Chronic Airflow Obstructions or Chronic Airflow Obstruction).ti,ab,kw. (127578)
3 1 or 2 (173884)
4 exp diet therapy/ (367315)
5 exp nutrition/ (2327179)
6 exp food/ (1091213)
7 exp diet/ (348654)
8 (Diet or Nutrition* or Food or Vegetable* or Fruit* or Nut or Nuts or Protein* or Amino Acid* or Fatty acid* or Micronutrient* or Phytochem* or Vitamin* or Minerals* or Antioxidant* or Carbohydrate*).ti,ab,kw. (5791505)
9 (fiber or probiotic* or omega).ti,ab,kw. (275021)
10 4 or 5 or 6 or 7 or 8 (6967921)
11 ((respirator* or lung) and (inflammation or immune)).ti,ab,kw. (155498)
12 respiratory function.ti,ab,kw. (17904)
13 improved lung function.ti,ab,kw. (1433)
14 exacerbat*.ti,ab,kw. (180737)
15 11 or 12 or 13 or 14 (343733)
16 3 and 10 and 15 (6649)
17 limit 16 to "therapy (best balance of sensitivity and specificity)" (724)
18 limit 16 to "therapy (maximizes sensitivity)" (1435)
19 limit 16 to "therapy (maximizes specificity)" (259)
20 4 or 5 or 6 or 7 or 8 or 9 (7131632)
21 3 and 15 and 20 (6700)
22 21 not 16 (51)
23 limit 22 to "therapy (maximizes sensitivity)" (8)

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Text S4: Additional search in Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to August 25, 2021>
Search Strategy:
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1 exacerbat*.ti,ab,kw. (118796)
2 improved lung function.ti,ab,kw. (749)
3 respiratory function.ti,ab,kw. (12275)
4 ((respirator* or lung) and (inflammation or immune)).ti,ab,kw. (96883)
5 1 or 2 or 3 or 4 (222291)
6 (Chronic Obstructive Pulmonary Disease or COPD or COAD or Chronic Obstructive Airway Disease or Chronic Obstructive Lung Disease or Chronic Airflow Obstructions or Chronic Airflow Obstruction).ti,ab,kw. (73007)
7 exp Pulmonary Disease, Chronic Obstructive/ (60078)
8 6 or 7 (94015)
9 (fiber or probiotic* or omega).ti,ab,kw. (242082)
10 (Diet or Nutrition* or Food or Vegetable* or Fruit* or Nut or Nuts or Protein* or Amino Acid* or Fatty acid* or Micronutrient* or Phytochem* or Vitamin* or Minerals* or Antioxidant* or Carbohydrate*).ti,ab,kw. (4832573)
11 exp Diet Therapy/ (57754)
12 Nutrition Therapy/ (2768)
13 exp "Diet, Food, and Nutrition"/ (1805333)
14 10 or 11 or 12 or 13 (5780591)
15 5 and 8 and 14 (3367)
16 limit 15 to "therapy (best balance of sensitivity and specificity)" (244)
17 limit 15 to "therapy (maximizes specificity)" (142)
18 limit 15 to "therapy (maximizes sensitivity)" (1347)
19 9 or 10 or 11 or 12 or 13 (5930008)
20 5 and 8 and 19 (3401)
21 limit 20 to "therapy (maximizes sensitivity)" (1358)
22 21 not 18 (11)

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Table S1: Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Quality
Ahnfeldt-Mollerup, P., et al. (2015). "**The effect of protein supplementation on quality of life, physical function, and muscle strength in patients with chronic obstructive pulmonary disease.**" European journal of physical and rehabilitation medicine **51**(4): 447-456 [19].	Low	Low	Unclear	Low	High	High	Low	**Poor**
Al-Azzawi, M. A., et al. (2020). "**Therapeutic effects of black seed oil supplementation on chronic obstructive pulmonary disease patients: A randomized controlled double blind clinical trial**." Heliyon **6**(8): e04711 [25].	Unclear	Unclear	Low	High	High	Unclear	Low	**Poor**
Baldrick, F. R., et al. (2012). "**Effect of fruit and vegetable intake on oxidative stress and inflammation in COPD: a randomised controlled trial**." The european respiratory journal **39**(6): 1377-1384 [23].	Low	Low	Unclear	Low	Low	Low	Low	**Fair**
Behnia M, Wheatley CM, Avolio A, Johnson BD. **Influence of dietary nitrate supplementation on lung function and exercise gas exchange in COPD patients**. Nitric Oxide. 2018 jun 1;76:53-61 [21].	Unclear	Unclear	Low	Low	Low	Unclear	Low	**Poor**
Constantin D, Menon MK, Houchen-Wolloff L, Morgan MD, Singh SJ, Greenhaff P, Steiner MC: **Skeletal muscle molecular responses to resistance training and dietary supplementation in COPD**. *Thorax* 2013, **68**(7):625-633 [29].	Low	Low	Low	Low	Low	Unclear	Low	**Fair**
Keranis E, Makris D, Rodopoulou P, et al. **Impact of dietary shift to higher-antioxidant foods in COPD**: a randomised trial. *Eur Respir J*. 2010;**36**(4):774-780 [24].	Low	Low	Low	low	High	Low	Low	**Fair**
Kerley CP, James PE, McGowan A, Faul J, Cormican L: **Dietary nitrate improved exercise capacity in COPD but not blood pressure or pulmonary function: a 2 week, double-blind randomised, placebo-controlled crossover trial**. *Int J Food Sci Nutr* 2019, **70**(2):222-231 [20].	Low	Low	Low	Low	Low	Low	Low	**Good**
Knowles JB, Fairbarn MS, Wiggs BJ, Chan-Yan C, Pardy RL. **Dietary supplementation and respiratory muscle performance in patients with COPD.** *Chest*.1988, **93**(5):977-983 [30].	Low	Low	Low	Low	Low	Low	Low	**Good**
Muhamad, R., et al. (2018). "**The effect of Tualang honey on the quality of life of patients with chronic obstructive pulmonary disease**: a randomized controlled trial." Journal of	Low	Low	Unclear	Low	Unclear	Unclear	Low	**Fair**

taibah university medical sciences **13**(1): 42-50 [26].								
Steiner MC, Barton RL, Singh SJ, Morgan MD. **Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial.** *Thorax* 2003, **58**(9):745-751 [31].	Low	Low	Low	Low	Low	Low	High	**Fair**
Sugawara K, Takahashi H, Kashiwagura T, Yamada K, Yanagida S, Homma M, Dairiki K, Sasaki H, Kawagoshi A, Satake M *et al*: **Effect of anti-inflammatory supplementation with whey peptide and exercise therapy in patients with COPD**. *Respir Med* 2012, **106**(11):1526-1534 [28].	Unclear	Low	Low	Low	High	Unclear	Low	**Poor**
Panahi, Y., et al. (2012). "**Impact of Adjunctive Therapy with Chlorellav ulgaris Extract on Antioxidant Status, Pulmonary Function, and Clinical Symptoms of Patients with Obstructive Pulmonary Diseases**." Scientia Pharmaceutica **80**(3): 719-730 [27].	Unclear	Unclear	Unclear	Low	High	Unclear	Low	**Poor**
Pavitt, M. J., et al. (2020). "**Oral nitrate supplementation to enhance pulmonary rehabilitation in COPD: ON-EPIC a multicentre, double-blind, placebo-controlled, randomised parallel group study**." Thorax. 2020 Jul;75(7):547-555 [22].	Low	Low	Low	Low	Low	Low	Low	**Good**

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Table S2: Extracted data (with added detail)

Study	Design	Population	Intervention	Outcome measures	Results
Ahnfeldt-Mollerup, P. et al., 2015: *The effect of protein supplementation on quality of life, physical function, and muscle strength in patients with chronic obstructive pulmonary disease* [19].	Prospective, parallel group randomized clinical trial	53 participants with stable moderate to severe COPD at outpatient rehabilitation	*I (n=28/18):* Two protein bars daily, each containing 135 kcal, 9.3 g protein, 14.6 g carbohydrate and 4.2 g fat. Also added linseed oil and tocopherol. *C (n=25/17):* no placebo *Both*: 2x/week physiotherapist supervised exercise classes, 1x/week unsupervised at-home training. *Duration*: 9 weeks. Follow-up at 9, 21 and 35 weeks.	**Physical function**: Shuttle walk time (s), mean treatment effect (95% CI)	*End-of-intervention:* -2.3 (-40, 44), p=ns
				Physical function: Maximal muscle strength test (N/kg), mean treatment effect (95% CI)	*End-of-intervention:* -0.05 (-0.57, 0.35), p=ns *End-of-follow-up:* -0.09 (-0.45, 0.63), p=ns
				Perceived health: SGRQ score, mean treatment effect (95% CI)	*End-of-intervention:* -2.3 (-12, 7), p=ns *End-of-follow-up:* -1.2 (-9, 11), p=ns
				Inflammatory marker: C-reactive protein (mg/l), mean treatment effect (95% CI)	*End-of-intervention:* 3.9 (-1.3, 9.2), p=ns
				Inflammatory marker: Leucocytes (10^9/L), mean treatment effect (95% CI)	*End-of-intervention:* -0.5 (-1.8, 0.9), p=ns
				SUMMARY	No significant differences between groups on all outcome measures at end-of-intervention and 6-month follow-up.
Al-Azzawi, M. A. *Et al., 2020: Therapeutic effects of black seed oil supplementation on chronic obstructive pulmonary disease patients: A*	Prospective, randomized controlled double-blinded clinical trial.	100 participants with mild to moderate COPD at outpatient setting.	*I (n=50/47):* 2x/day capsules containing 1 g cold-pressed black seed oil *C (n=50/44):* no placebo	**Lung function:** FEV1 (% of predicted), pre-post mean ± SD.	I: 74±9.0 – 82±6.9 (p<0.001) C: 73±8.4 - 76±7.8 (p=0.06) Significant improvement for I compared to C, p<0.001.
				Lung function: FVC (% of predicted), pre-post mean ± SD	I: 83±8.2 – 91±8.0 (p<0.001) C: 83±8.4 – 85±9.1 (p=0.14) Significant improvement for I compared to C, p=0.002

randomized controlled double blind clinical trial [25].			*Duration*: 3 months	**Lung function:** FEV1/FVC (% of predicted), pre-post mean ± SD	I: 67±0.70 – 75±0.64 (p=0.012) C: 69±7.2 – 71±7.6 (p=0.08) Significant improvement for I compared to C, p=0.001.
				Lung function: PEF (% of predicted), pre-post mean ± SD	I: 55±6.4 – 65±5.3 (p<0.001) C: 53±4.7 – 56±6.6 (p=0.14) Significant improvement for I compared to C, p<0.001.
				Lung function: FEF_{25-75} (% of predicted), pre-post mean ± SD	I: 29±3.2 – 35±5.2 (p<0.001) C: 28±3.3 – 29±3.5 (p=0.07) Significant increase for I compared to C, p<0.001
				Inflammatory marker: Plasma TNF-α (pg/ml), pre-post mean ± SD.	I: 33±3.0 – 22±5.1 (p<0.001) C: 34±2.5 – 26±5.0 (p<0.001) Significant decrease for I compared to C, p<0.001
				Inflammatory marker: Plasma IL-6, pre-post mean ± SD.	I: 4.1±0.5 - 2.5±0.6 (p<0.001) C: 4.0±0.5 - 3.1±0.6 (p<0.001) Both groups decreased, I more than C. Between-group p-value not given.
				Oxidative stress marker: Thiobarbituric acid reactive substances (nmol MDA/ml), pre-post mean ±S D	I: 7.2±1.2 - 3.8±0.7 C: 6.7±1.3 - 6.2±1.3 Significant decrease for I compared to C, p<0.001
				Oxidative stress marker: Protein carbonyl content (nmol/mg protein), pre-post mean ± SD.	I: 3.0±0.56 - 2.0±0.52 C: 2.9±0.46 - 2.7±0.48 Significant decrease for I compared to C, p<0.001
				Antioxidant marker: Catalase (nmol/min/ml), pre-post mean ± SD.	I: 58±3.5 – 78±7.0 C: 61±5.7 – 63±4.6 Significant decrease for I compared to C, p<0.001

				Antioxidant marker: Glutathione peroxidase (nmol/min/ml), pre-post mean ± SD.	I: 51±2.2 – 69±2.7 C: 53±1.3 – 55±2.6 Significant increase only for I, p<0.001.
				Antioxidant marker: Superoxide dismutase (U/ml), pre-post mean ± SD.	I: 3.0±0.81 - 4.0±1.2 C: 2.9±0.86 - 3.3±1.2 Significant increase in I compared to C, p=0.001.
				Antioxidant marker: Reduced glutathione (mg/dl), pre-post mean ± SD.	I: 14±4.5 – 20±7.3 C: 14±4.1 – 16±4.4 Significant increase in I compared to C, p=0.001.
				Antioxidant marker: Vitamin C (mg/dl), pre-post mean ± SD.	I: 0.36±0.02 - 0.60±0.02 C: 0.35±0.02 - 0.37±0.02 Significant increase in I compared to C, p<0.001.
				Antioxidant marker: Vitamin E (mg/dl), pre-post mean ± SD.	I: 0.54±0.02 - 0.88±0.02 C: 0.57±0.02 - 0.59±0.02 Levels elevated significantly only for I, p<0.001.
				SUMMARY	Significant differences favoring intervention over control on all outcome measures.
Baldrick, F. R. et al., 2012: *Effect of fruit and vegetable intake on oxidative stress and inflammation in COPD: a randomised controlled trial* [23].	Open-label randomized controlled trial	81 participants with stable moderate to severe COPD and habitually low fruit and vegetable intake (≤2 portions*) at outpatient setting. * 80-g serving of fruit or vegetable, or 150 mL of fruit juice	*I (n=40/38):* ≥5 portions of fruits and vegetables daily. *C (41/37)*: ≤2 portions of fruits and vegetables daily. *Both:* weekly self-selected deliveries of fruits and vegetables. Advise on storage and cooking methods. Weekly contact by study researcher to	**Lung function:** FEV1 (% of predicted), change from baseline	I: +2% (p=0.552) C: +3% (p=0.288) No significant between-group difference, p=0.654
				Lung function: FVC (% of predicted), change from baseline	I: +2% (p=0.356) C: +9% (p=0.032) No significant between-group difference, p=0.142
				Lung function: FEV1/FVC (% of predicted), change from baseline	I: -2% (p=0.484) C: -5% (p=0.103) No significant between-group difference, p=0.306
				Inflammatory marker: Sputum Interleukin-8 (ng/ml), change from baseline	I: -15% (p=0.407) C: -15% (p=0.538) No significant between-group difference, p=0.992

			encourage compliance. *Duration*: 12 weeks Assessment at 6 and 12 weeks.	**Inflammatory marker**: Sputum myeloperoxidase (ng/ml), change from baseline	I: +14% (p=0.427) C: -1% (p=0.945) No significant between-group difference, p=0.500
				Inflammatory marker: Sputum neutrophil elastase (mig/ml), change from baseline	I: -21% (p=0.453) C: -41 % (p=0.348) No significant between-group difference, p=0.621
				Inflammatory marker: Plasma CRP (mg/l), change from baseline	I: +21% (p=0.219) C: -18% (p=0.309) No significant between-group difference, p=0.116
				Oxidative stress marker: Urine 8-isoprostane (nM/mM creatinine), change from baseline	I: -6% (p=0.353) C: -8% (p=0.104) No significant between-group difference, p=0.806
				Oxidative stress marker: Sputum 8-isoprostane (ng/ml), change from baseline	I: +27% (p=0.302) C: -8% (p=0.743) No significant between-group difference, p=0.334
				SUMMARY	No significant within-group or between-group findings for any outcome measures, except for an increase in FVC (%pred) for control group (+9%, p=0.032)
Behnia, M. et al., 2018: *Influence of dietary nitrate supplementation on lung function and exercise gas exchange in COPD patients* [21].	Randomized, parallel, placebo-controlled, single-blind trial	25 patients with stable mild to severe COPD at outpatient clinic.	*I (n=12):* 1x/day 80 ml beetroot juice mixed with 180 ml blackcurrant juice. *C (n=13):* 1x/day 80 ml water mixed with 180 ml black currant juice *Duration*: 8 days	**Lung function**: FVC, change from baseline (%)	I: +1 (p=ns) C: +1 (p=ns) No significant difference between groups.
				Lung function: FEV1, change from baseline (%)	I: -1 (p=ns) C: -3 (p=ns) No significant difference between groups.
				Lung function: FEV1 /FVC, change from baseline (%)	I: 0 (p=ns) C: 0 (p=ns)

				Lung function: $FEF_{25-75,}$ change from baseline (%)	I: -5 (p=ns) C: +15 (p=ns) No significant difference between groups.
				Lung function: FEF_{75}, change from baseline (%)	I: -5 (p=ns) C: +17 (p=ns) No significant difference between groups.
				Respiratory muscle: Maximal voluntary ventilation, change from baseline (%)	I: +2 (p=ns) C: +1 (p=ns) No significant difference between groups.
				Resting lung diffusing capacity: Single breath lung diffusing capacity (SBDLCO, ml/min/mmHg), intra-breath lung diffusing capacity (IBDLCO, ml/min/mmHg), IBDLCO/SBDLCO (%)	No significant difference between group on any measures.
				Exercise lung diffusing capacity: IBDLCO (ml/min/mmHg), exercise IBDLCO/resting IBDLCO (%)	No significant differences within or between groups on any measures
				Exercise capacity: Work (W), Oxygen consumption ($VO_{2,}$ ml/kg/min) *During submaximal and maximal exercise.*	No significant differences within or between groups on any measures
				Ventilation parameters: Ventilation (VE, L/min), Tidal volume (TV, L), Breathing frequency	No significant differences within or between groups on any measures.

				(bpm), Inspiratory capacity (IC, L), VY/IC, VE/IC, VE/breathing capacity (%) *During submaximal and maximal exercise.*	
				Gas exchange parameters: VE/VO_2 ratio, P_{etCO2} (mmHg), PE_{CO2} (mmHg), PE_{CO2}/Pet_{CO2} ratio, estimate of vascular capitance (GXCap) *During submaximal and maximal exercise.*	No significant differences within or between groups on any measures.
				Perceived health: SGRQ, change (%)	I: -17 ($p<0.05$) C: -4.2 (p=ns) No significant difference between groups.
				Dyspnea: Borg RPE during submaximal exercise, change (%)	I: 0 (p=ns) C: 0 (p=ns)
				Dyspnea: Borg RPE during maximal exercise, change (%)	I: 0 (p=ns) C: 0 (p=ns)
				Dyspnea: Dyspnea during submaximal exercise, change (%)	I: 0 (p=ns) C: 0 (p=ns)
				Dyspnea: Dyspnea during maximal exercise, change (%)	I: 0 (p=ns) C: 0 (p=ns)
				SUMMARY	Significantly decreased perceived impairment in health (SGQR) in the intervention group at end-of-intervention. Difference between the groups not significant. No significant changes within or between groups on any other outcome measures.

Constantin, D. et al., 2013: *Skeletal muscle molecular responses to resistance training and dietary supplementation in COPD* [29].	Randomized, parallel, placebo-controlled, double-blind trial	59 patients with stable, severe to very severe COPD	*I (n=32/25):* 3/week nutrition drink (containing 19 g protein and 49 g glucose polymer carbohydrate in 500 ml of water) immediately after training session. *C (n=27/25):* noncaloric placebo drink *Both*: 3/week supervised resistance training *Duration*: 8 weeks. Assessment at 4 and 8 weeks.	**Physical function:** Quadriceps muscle function, isometric strength (change from baseline (% ± SEM)	*At 4 weeks:* I: 14.6±2.8 (p<0.001) C: 16.9±4.3 (p<0.01) *At 8 weeks:* I: 18.0±3.4 (p<0.001) C:17.7±3.7 (p<0.001)
				Physical function Isokinetic work, 180 degrees/s (J)	Improvement for both I and C. No significant difference between groups.
				SUMMARY	Significant increase in quadriceps muscle function and isokinetic work in both groups. Between-group differences not significant.
Keranis E. et al, 2010: *Impact of dietary shift to higher-antioxidant foods in COPD: a randomised trial* [24].	Randomized controlled single-blinded trial	120 participants with stable COPD from community-based outpatient clinic. Male/females n=105/15.	*Both*: Scheduled visits at outpatient clinics every 6 months attended by two members of the research team. *I (N=60):* Informed on benefits of an antioxidant-rich diet with increased fruit and vegetable consumption upon outpatient clinic visits. Advised to increase their fruit/fruit juice/vegetable consumption by 1 portion/day compared	**Lung function:** FEV1 (% of predicted).	Annual increase for I (~ +8%), whereas C had a decline (~+15 %), p=0.03
				Fruit and vegetable consumption, as well as consumption of other food categories, was assessed through a questionnaire	I increased their consumption of fruits and vegetables significantly compared to C, p<0.001.
				SUMMARY	Significant annual improvement in FEV1 for I, decline for C.

			to baseline. *C (N=60):* no discussion of dietary issues during visits at outpatient clinic. *Duration*: 3 years. Assessment at every 6 months.		
Kerley P. et al., 2019: *Dietary nitrate improved exercise capacity in COPD but not blood pressure or pulmonary function: a 2 week, double-blind randomised, placebo-controlled crossover trial* [20].	Randomized, crossover, placebo-controlled, double-blind trial	10 participants with stable COPD from outpatient clinic	*I (10/8):* 1/day 140 ml beetroot juice *C (10/8):* 1/day 140 ml nitrate depleted beetroot juice Duration: 14 days each period. No washout. Assessment at end of each study period.	**Lung function**: FEV1 (% of prediced, mean±SD)	*Baseline*: 57±19 *I at end-point:* 57±21 *C at end-point*: 55±19 Difference between I and C: p=0.14
				Lung function: FVC (% of prediced, mean±SD)	*Baseline*: 91±12 *I at end-point:* 102±23 *C at end-point:* 93±16 Difference between I and C: p=0.14
				Perceived health: Clinical COPD Questionnaire	No significant difference
				Dyspnea: Dyspnea score during ISWT	No significant difference
				Physical function: leg fatigue score during ISWT	No significant difference
				Physical function: ISWT distance walked (m, mean ± SD)	*Baseline*: 384±163 *I at end-point* Post: 440±161 *C at end-point*: Post: 396±156 Difference between I and C: p<0.001
				SUMMARY	Significant improvement on ISWT for I compared to C. No significant differences between groups on other outcome measures, including lung function parameters and

					outcomes assessing perceived health.
Knowles J. et al., 1988: *Dietary supplementation and respiratory muscle performance in patients with COPD* [30].	Randomized observer-blinded crossover trial	25 participants with stable severe COPD at outpatient setting	*I (n=25):* Powdered supplement containing 24% protein, 22% fat and 54 % carbohydrates (Sustacal®). Increasing caloric intake by 50% daily. *C (n=25):* no placebo *Duration*: 8 weeks for each crossover phase	**Lung function**: FEV1 (% predicted, mean±SD)	Group A *Baseline*: 37±12 *Intervention*: 36±14 *Control*: 40±12 Group B *Baseline*: 40±14 *Intervention*: 39±17 *Control*: 36±11
				Lung function: FVC (% predicted, mean±SD)	Group A *Baseline*: 73±21 *Intervention*: 67±18 *Control*: 76±23 Group B *Baseline*: 65±16 *Intervention*: 68±17 *Control*: 66±17
				Inflammatory marker: serum lymphocytes (count/µL)	Group A *Baseline*: 1516±645 *After-intervention*: 1720±635 Group B *Baseline*: 1789±746 *After-intervention*: 1681±710
				Respiratory muscle performance: Maximal static inspiratory pressure at the mouth (PImax), maximal expiratory pressure at the mouth after maximal inspiration (PEmax), sustainable inspiratory pressure (SIP), pressure time product (PTP)	No significant differences on any outcomes.
				SUMMARY	No significant differences on outcome measures including lung function parameters, respiratory

					muscle function and lymphocyte count.
Muhamad R. et al., 2018: *The effect of Tualang honey on the quality of life of patients with chronic obstructive pulmonary disease: a randomized controlled trial* [26].	Single-blinded randomized controlled trial	60 male participants with COPD at outpatient setting	*I (30/22):* 1/day sacket with 20 mg Tualang honey. Advised to consume before breakfast. *C (n=30/12):* no placebo *Duration*: 6 months. Assessment at 2, 4 and 6 months.	**Perceived health:** SGRQ total score, mean change from baseline (95% CI)	I: 48 (40, 55) – 23 (15, 31) C: 48 (38, 58) – 42 (31, 53) Difference between groups: p=0.001
				Perceived health: SGRQ symptom domain score, mean change from baseline (95% CI)	I: 47 (37, 56) – 22 (13, 31) C: 49 (36, 63) – 34 (22, 47) Difference between groups p=0.677
				Perceived health: SGRQ activity domain score, mean change from baseline (95% CI)	I: 68 (58, 78) – 34 (24, 44) C: 67 (53, 81) – 62 (49, 76) Difference between groups p=0.001
				Perceived health: SGRQ impact domain score, mean change from baseline (95% CI)	I:37 (30, 45) – 17 (9.0, 25) C:37 (27, 46) – 33 (22, 43) Difference between groups p=0.001
				FEV1(l), pre-post median	I: 1.23– 1.25, p=0.013 C: 1.25–0.96, p=0.009
				FVC(l), pre-post median	I: 2.26-2.23, p=0.031 C: 2.17-2.27, p<0.001
				FEV1/FVC (%), pre-post median	I: 59.2-59.0, p=0.199 C: 57.2-51.0, p=0.362
				FEF_{25-75}(%), pre-post median	I: 0.70-0.58, p=0.215 C: 0.54-0.45, p=0.179
				SUMMARY	Improved perceived health (SGRQ) for I compared to C on total score and on all subdomains except for symptom domain. Non-significant between-group changes in lung parameters.
Panahi Y. et al., 2012: *Impact of Adjunctive Therapy with Chlorellav ulgaris Extract on Antioxidant*	Randomized open-label clinical trial	97 participants with stable moderate to severe COPD	*I (n=48/28):* 2700 mg of Chlorella vulgaris extract daily in the	**Lung function:** FEV1 (% of predicted), FVC (% of predicted), FEV1/FVC (%), FEF_{25-75} (%)	No significant changes in FVC, FEV1/FVC or FEF_{25-75} from baseline to end-point for either group. For FEV1 control group had

Status, Pulmonary Function, and Clinical Symptoms of Patients with Obstructive Pulmonary Diseases [27].			form of tablets *C (n=49/29*): no placebo. *Duration*: 8 weeks.		a significant improvement from baseline (p=0.03).
				Antioxidant status: Vitamin E, magnitude of change ± SD	I: 2.78±15.9 C: 0.05±0.25 Difference between groups: p<0.001
				Antioxidant status: Vitamin C, magnitude of change±SD	I: 0.46±0.34 C: −0.04±0.20 Difference between groups: p<0.001
				Antioxidant status: Glutathione, magnitude of change±SD	I: 9.4±2.3 C: 2.6±5.2 Difference between groups: p<0.001
				Antioxidant status: Malonedialdehyde, magnitude of change±SD	I: -2.0±0.86 C: −0.60±1.5 Difference between groups: p=0.025
				Antioxidant status: Glutathione peroxidase, magnitude of change±SD	I: 2.3±0.44 C: 0.15±1.1 Difference between groups: p<0.001
				Antioxidant status: Catalase, magnitude of change±SD	I: 10.5±5.0 C: −1.7±5.3 Difference between groups: p<0.001
				Antioxidant status: Superoxide dismutase, magnitude of change±SD	I: 1.0±0.56 C: 0.60±0.78 Difference between groups: p=0.011
				Antioxidant status: Total antioxidant status, magnitude of change±SD	I: 0.30±0.24 C: 0.20±0.29 Difference between groups: p=ns
				Perceived health: SGRQ symptom domain	**SGRQ symptoms domain** <u>Coughing</u>

					Reduced for both groups, non-significant differences between I and C <u>Shortness of breath</u> Reduced for both groups, non-significant differences between I and C <u>Wheezing</u> Reduced for both groups, non-significant differences between I and C <u>Sputum production</u> Both groups improved, significantly greater improvement for I (p=0.02).
				SUMMARY	Improved antioxidant status for all measures (except TAS) for I compared to C. No significant differences on lung function parameters. No significant findings on symptom domain, expect for the item om sputum production where I had a slight improvement compared to C.
Pavitt M. J. et al., 2020: *Oral nitrate supplementation to enhance pulmonary rehabilitation in COPD: ON-EPIC a multicentre, double-blind, placebo-controlled, randomised parallel group study* [22].	Randomized, placebo controlled, double blinded trial	165 participants with stable moderate to severe COPD	*I (78/57):* 140 ml of a beetroot juice product containing 0.8 g of nitrate consumed 3 h before PR sessions *C (87/65):* 140 ml nitrate depleted beetroot juice Both: PR program consisting of 2x/week supervised exercise and home based	**Physical function:** Incremental shuttle walk test (estimated treatment effect (95% CI))	30 m (10, 40), p = 0.027
				Perceived health: COPD assessment test (estimated treatment effect (95% CI))	0 (-1,3), p=0.74
				Dyspnea: MRC dyspnea score (estimated treatment effect (95% CI))	0 (0,0), p=0.90

			exercises Duration: 8 weeks	**Physical function:** Daily step count (estimated treatment effect (95% CI)) *Sample reduced to I: 28, C: 37	784 steps/day (100, 1471), p=0.02
				Physical function: physical activity level (estimated treatment effect (95% CI)) *Sample reduced to I: 28, C: 37	0.2 (-0.3, 0.7), p=0.73
				Physical function: time spent in activity >3 METs (estimated treatment effect (95% CI)) *Sample reduced to I: 28, C: 37	13 min/day (2, 28), p=0.02
				SUMMARY	Significant treatment effect on physical function measures including ISWT, daily steps and time spent in activity >3 METs. No significant difference between groups on dyspnea, perceived health or physical activity level.
Steiner M. C. et al., 2003: *Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial* [31].	Randomized placebo-controlled clinical trial	85 participants with stable COPD at outpatient setting	*I (42/25):* 3/day 125 ml nutritional drink (Respifor®) providing a total of 570 kcal daily (60 % carbohydrates, 20 % protein, 20 % fat) *C (43/35):* Non-nutritive placebo	**Physical function:** Incremental shuttle walk test (m, mean difference between groups (95% CI)) * for participants with BMI > 19	18 (-8, 45), p=0.174 *27 (1,53), p=0.041
				Physical function: Excremental shuttle walk test (m, mean	103 (-55, 255), p=0.182

			Both: 2/week pulmonary rehabilitation programme with endurance training as well as patient education Duration: 7 weeks	difference between groups (95% CI)) * for participants with BMI > 19	 *121 (-44, 286), p=0.129
				Physical function: Hand grip strength (kg force, mean difference between groups (95% CI)) * for participants with BMI > 19	0.95 (-0.04, 1.89), p=0.060 *0.85 (-0.26, 1.97), p=0.129
				Physical function: Quadriceps strength (N, mean difference between groups (95% CI)) * for participants with BMI > 19	16.5 (-1.2, 34.2), p=0.068 *16.5 (-3.1, 36.1), p=0.097
				SUMMARY	Non-significant differences between groups on outcome measures related to physical function. Sensitivity analysis of those with BMI > 19 revealed a small improvement on the ISWT for the intervention group compared to control.
Sugawara, K. et al, 2012: *Effect of anti-inflammatory supplementation with whey peptide and exercise therapy in patients with COPD* [28].	Randomized, parallel, controlled, un-blinded trial	36 patients with stable COPD and body weight < 110 % of ideal body weight.	*I (n=18/17):* 2/day 200 ml nutrition drink (MEIN™) containing 200 kcal, protein 20%, lipids 25%, sugars 53,2 % and food fibers 1,8%. Added whey peptide, n-3-fatty acids, vitamin A, C, and D. *C (n=18/14):* no placebo	**Respiratory muscle:** Maximum expiratory mouth pressure (cmH_2O, mean change ±SD)	I: 40.1±55.6, p=0.01 C: 8.8±36.0, p=ns Difference between groups: ns
				Respiratory muscle: Maximum inspiratory mouth pressure (cmH_2O, mean change ±SD)	I: 39,2±38,9 (p=0.0011) C: 0.1±24.1 (p=ns) Difference between groups: p=0.003
				Physical function: Weight bearing index; isometric extension and	I: 10.0±13.3 (p=0.0169) C: -1.6±9.5 (p=ns)

			Both: Pulmonary rehabilitation; dietary instructions, exercise, breathing training and COPD education. *Duration*: 12 weeks	contraction of quadriceps muscle (kg/kg, mean change % ±SD)	Difference between groups: p=0.0079
				Physical function: 6 minute walk test (m, mean change % ±SD)	I: 19.7±24.7 (p=0.004) C: -7.1±50.8 (p=ns) Difference between groups: p=0.0137
				Perceived health: Chronic respiratory disease questionnaure, total (CRQ score, mean change % ±SD)	I: 6.2±7.5 (p=0.0033) C: -2.7±13.1 (p=ns) Difference between groups: p=0.0374
				Perceived health: CRQ, dyspnea subscale (score, mean change % ±SD)	I: 10.8±26.8 (p=ns) C: -2.7±21.3 (p=ns) Difference between groups: ns
				Perceived health: CRQ, fatigue subscale (score, mean ±SD)	I: 8.3±17.9 (p=ns) C: -3.6±22.8 (p=ns) Difference between groups: ns
				Perceived health: CRQ, emotional subscale (score, mean ±SD)	Change: 8.9±14.4 (p=ns) C: -3.9±12.2 (p=ns) Difference between groups: p=0.0097
				Perceived health: CRQ, mastery subscale (score, mean change % ±SD)	I: 3.1±9.1 (p=ns) C: 3.6±20.8 (p=ns) Difference between groups: ns
				Dyspnea: MRC during 6MWT (score, mean change ±SD)	I: -4,4±17,2 (p=ns) C: 22,6±40,6 (p=ns-9 Difference between groups: p=0,0339
				Inflammatory marker: Interleukin 6 (pg/ml, mean change % ±SD)	I: -10.6±33.7 (p=ns) C: 16.5±29.4 (p=ns) Difference between groups: p=0.0268
				Inflammatory marker:	I: -32.7±101.3 (p=0.0332) C: 1.52±2.30 (p=ns)

				Interleukin 8 (pg/ml, mean change % ±SD)	Difference between groups: p=0.0021
				Inflammatory marker: High-sensitivity C-reactive protein (mg/ll, mean change % ±SD)	I: -22.6±41.8 (p=0.0357) C: 28.8±100.9 (p=ns) Difference between groups: p=0.0470
				Inflammatory marker: Tumor necrosis factor-α (pg/ml, change % ±SD)	I: -12.9±15.3 (p=0.0053) C: 4.4±20.5 (p=ns) Difference between groups: p=0.0112
				SUMMARY	Significant difference between groups in MIP, weight bearing index, 6MWT, CRQ (total and emotional subscale) and MRC during 6MWT. Significant reduction in inflammatory markers Il-6, Il-8, hsCRP and TNF-α for I compared to C. No significant difference in MEP or CRQ (dyspnea, fatigue and mastery subscales).

6MWT, six-minutes walking test; Borg RPE, Borg rating of perceived exertion; BMI, body mass index; CRP, C-reactive protein; DLCO, diffusing capacity in the lung for carbon monoxide; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; FEF, forced expiratory flow; hsCRP, high sensitivity CRP; IL-6, interleukin 6; IL-8, interleukin 8; ISWT, incremental shuttle walk test; MEP, maximal expiratory pressure; MET, metabolic equivalent of tast; MIP, maximal inspiratory pressure; MRC, medical research council; PEF, peak expiratory flow; SD, standard deviation; SGQR, St. Georges respiratory questionnaire