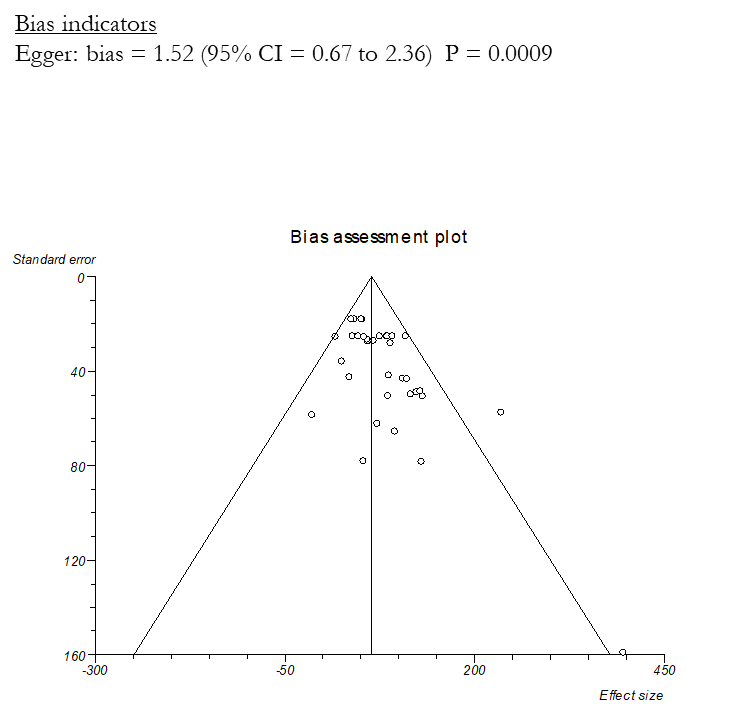
Long-acting bronchodilators improve exercise capacity in COPD patients: a systematic review and meta-analysis

Fabiano **Di Marco**1, Giovanni **Sotgiu**2, Pierachille **Santus**3, Denis E. **O’Donnell**4, Kai-Michael **Beeh**5, Simone **Dore**2, Maria Adelaide **Roggi**6, Lisa **Giuliani**1, Francesco **Blasi**7, and Stefano **Centanni**1

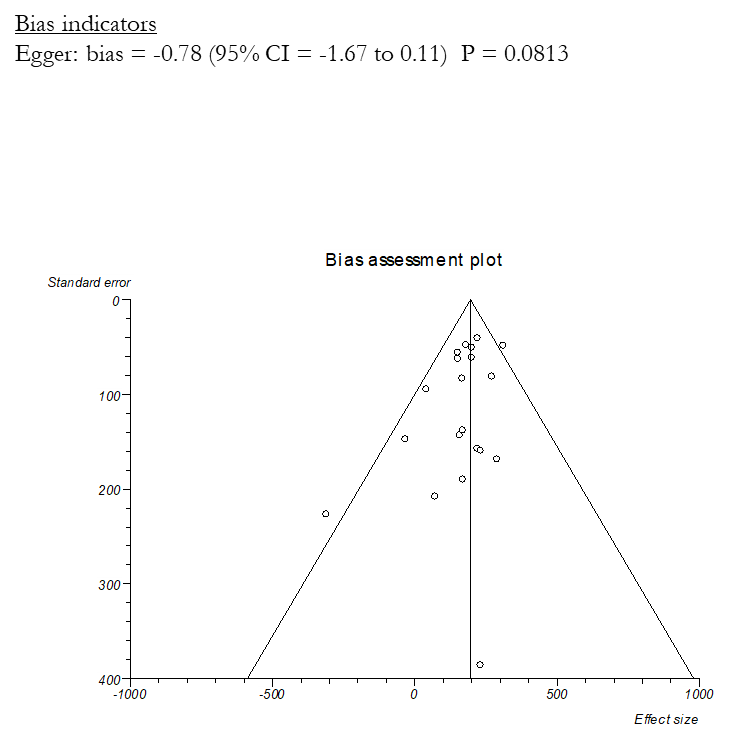
**Additional file**

**Figure S1.** Funnel plots for ET, isotime IC and isotime dyspnea (all studies).

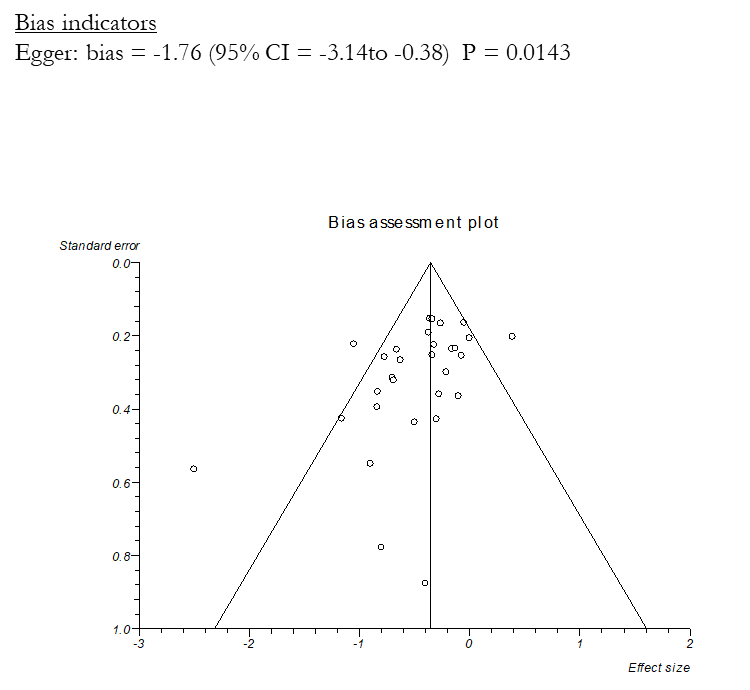
**Endurance time**

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**Isotime inspiratory capacity**

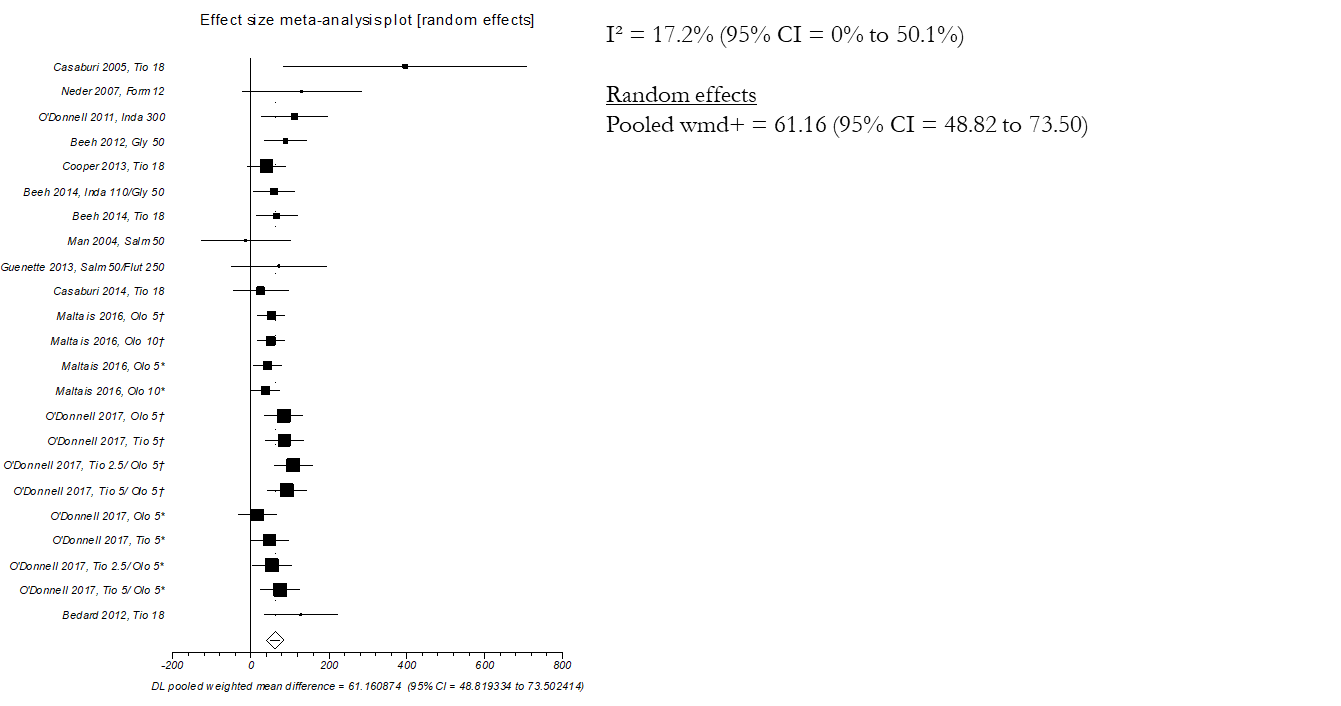
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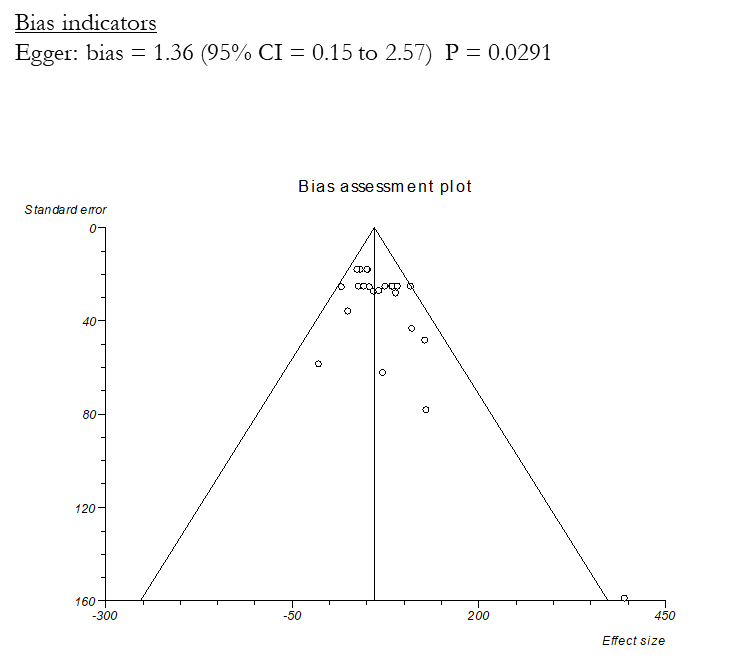
**Isotime dyspnea BORG**

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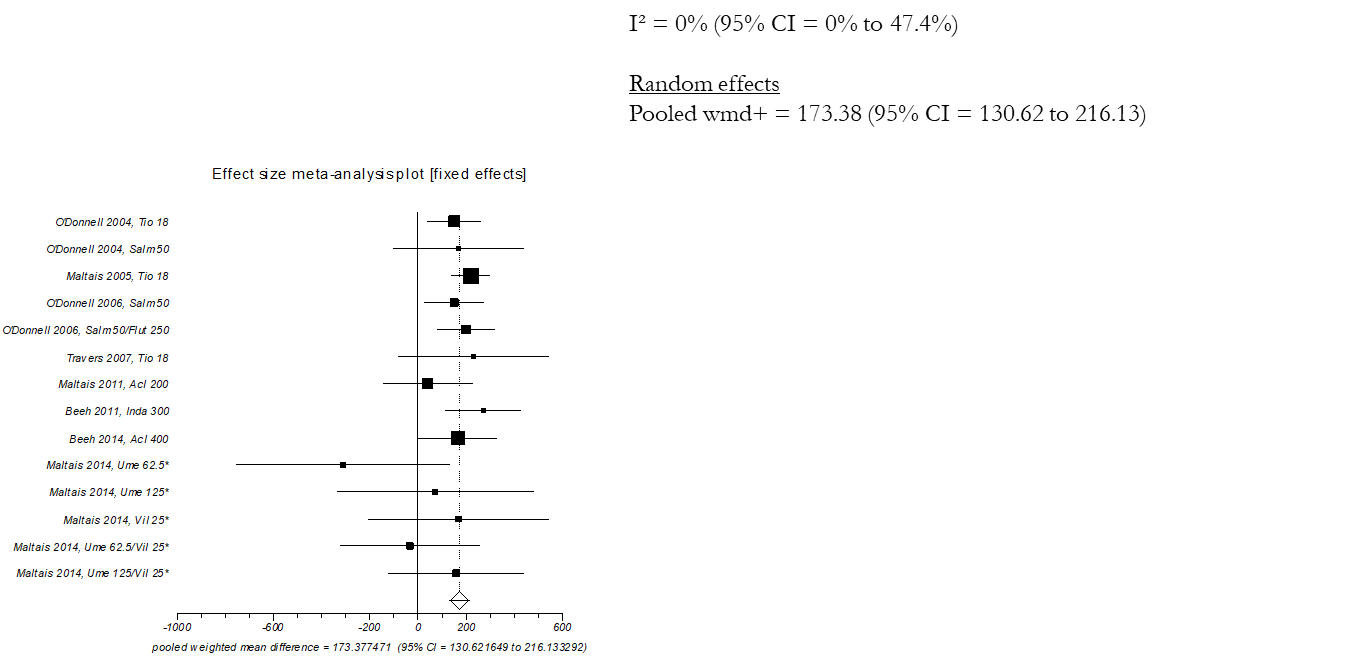
**Figure S2 A.** Forest and Funnel plots of ET, isotime IC and isotime dyspnea in the 11 studies which included only COPD patients with functional residual capacity (FRC) > 120%.

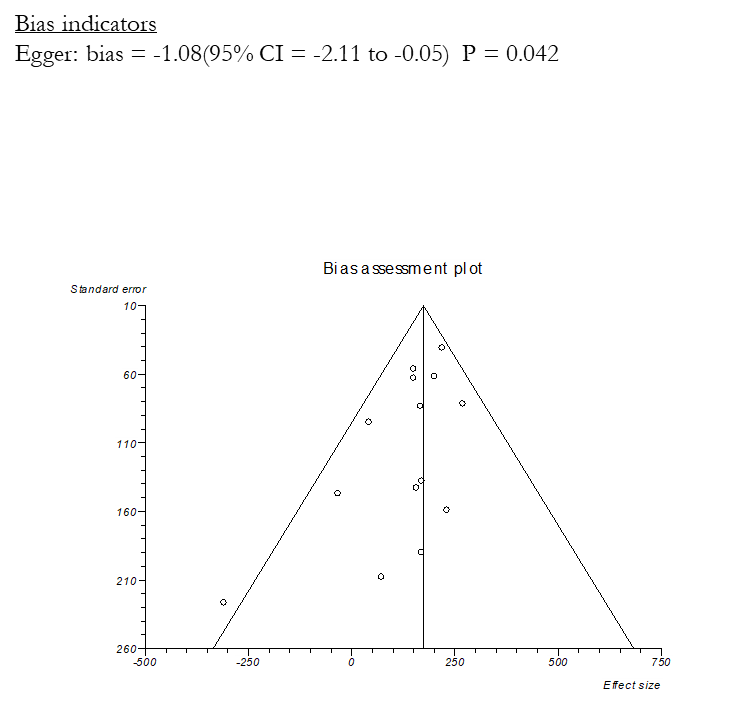
**Endurance time**

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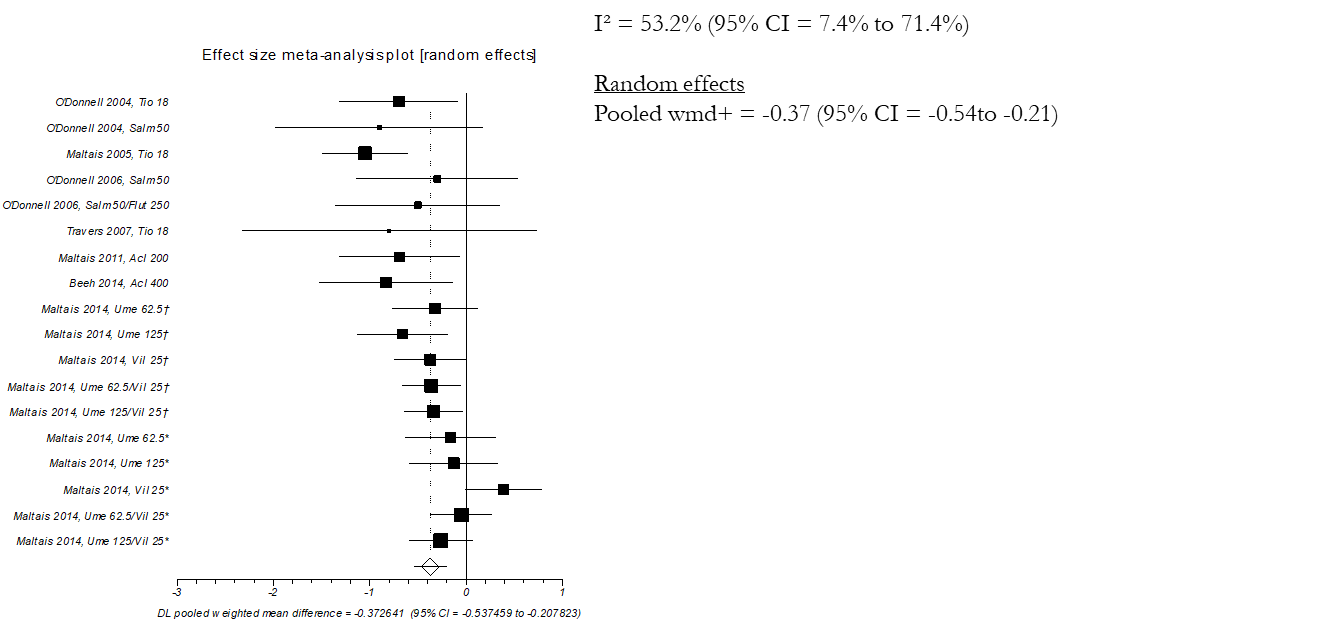
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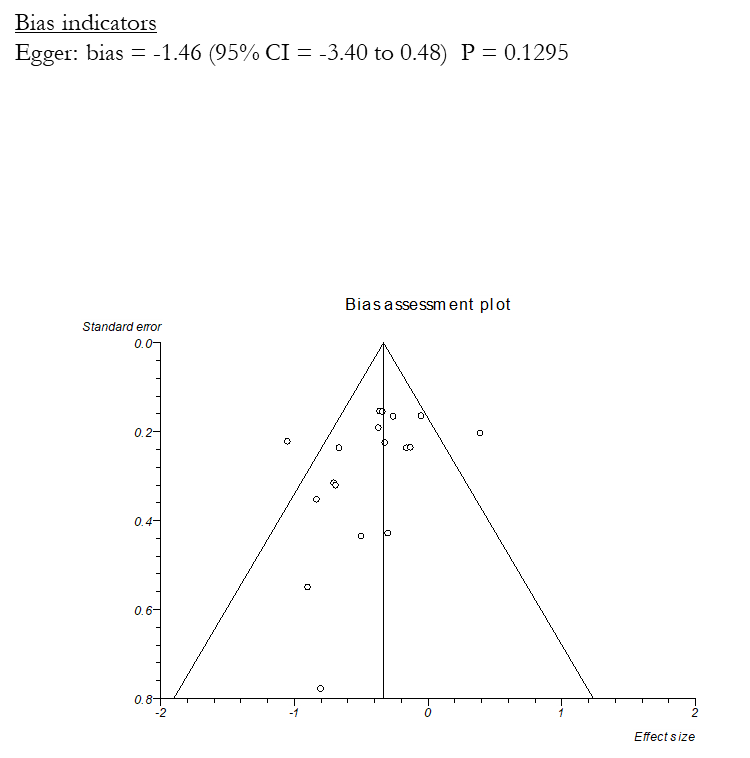
**Isotime inspiratory capacity**

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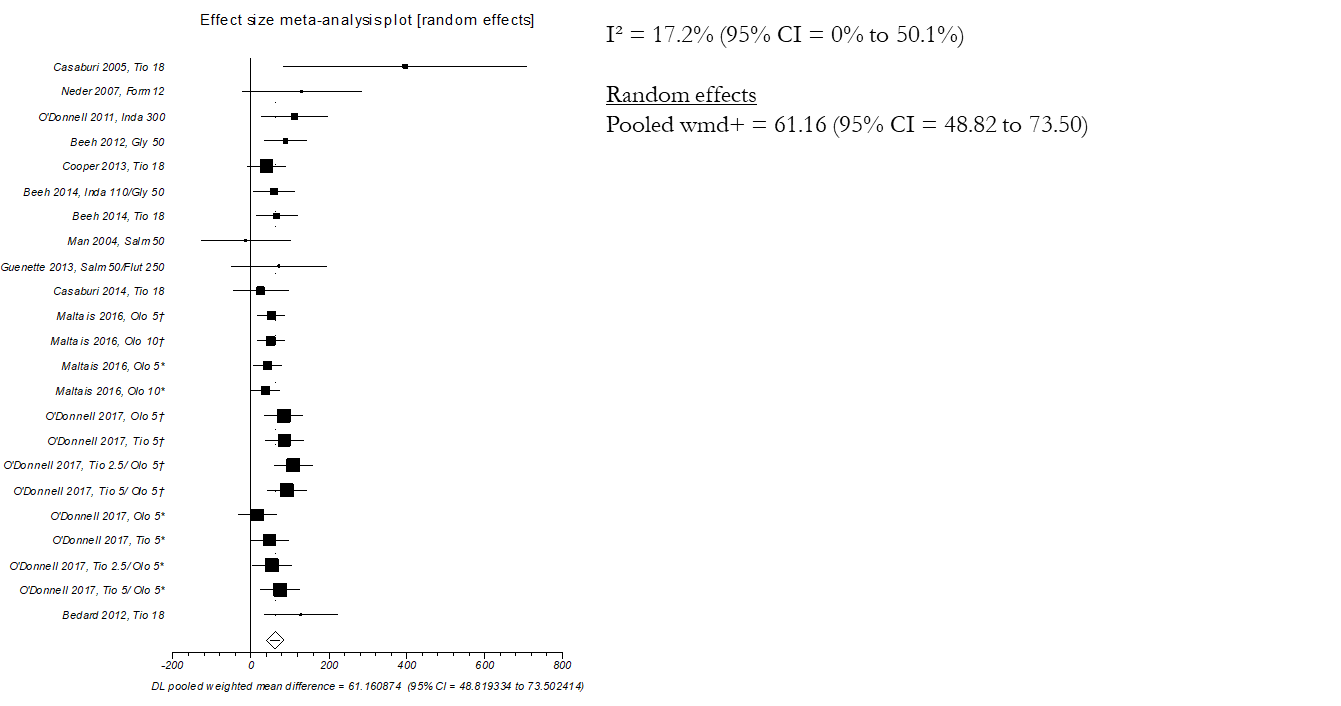
**Isotime dyspnea BORG**

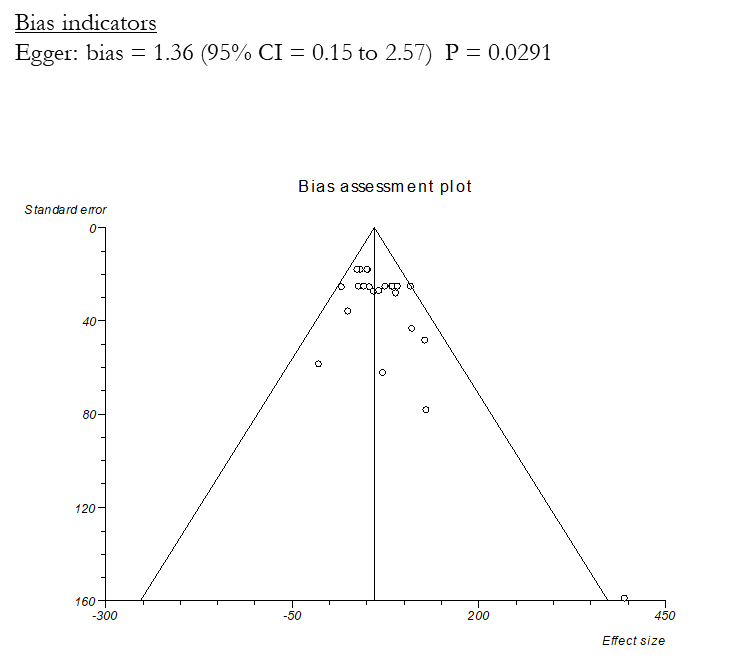
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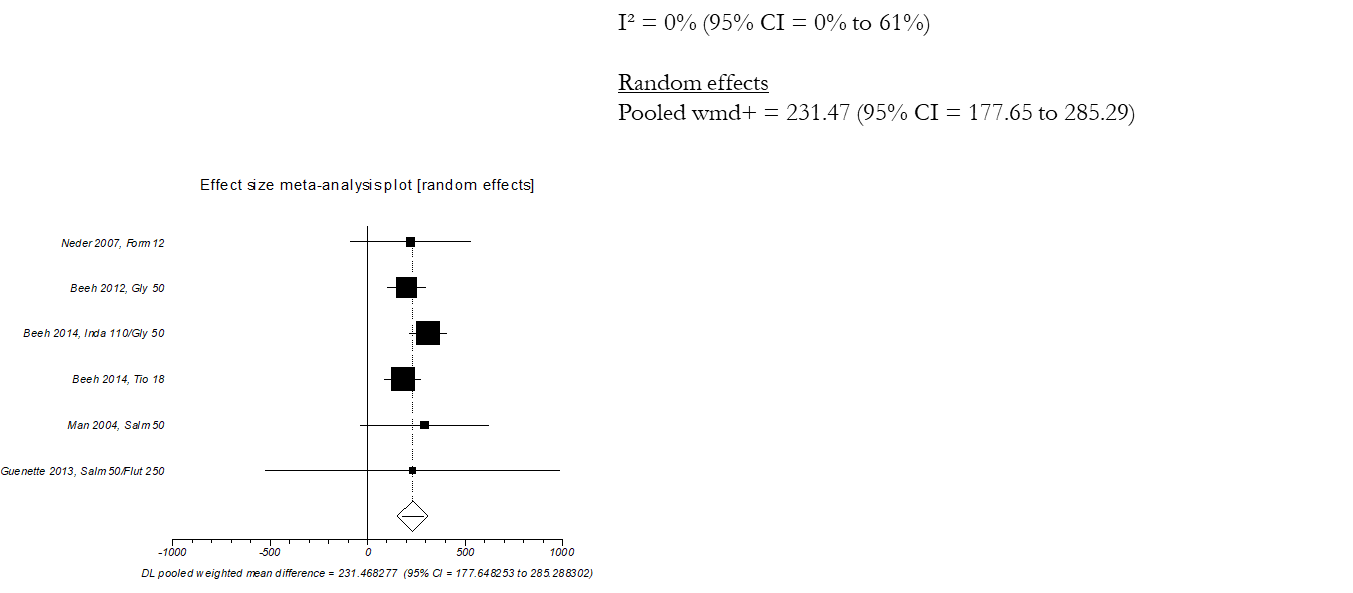
**Figure S2 B.** Forest and Funnel plots of ET, isotime IC and isotime dyspnea in the studies which did not require an increase of functional residual capacity (FRC) as inclusion criterion.

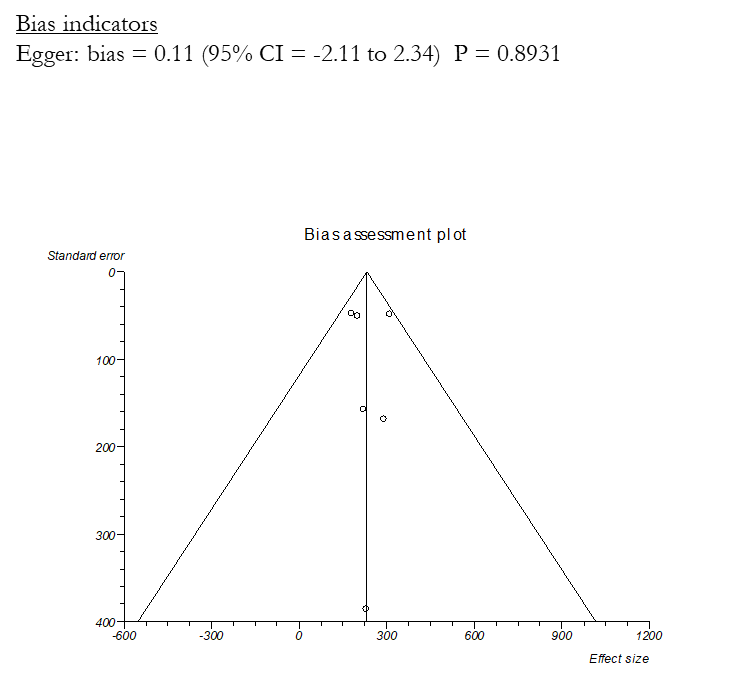
**Endurance time**

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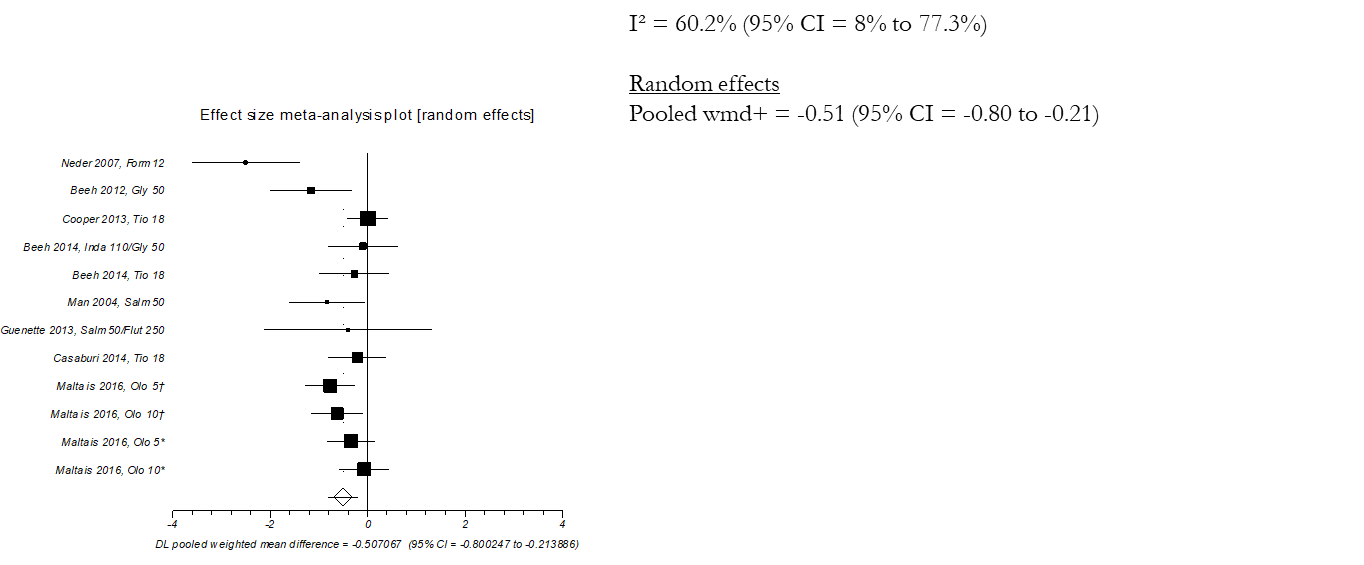
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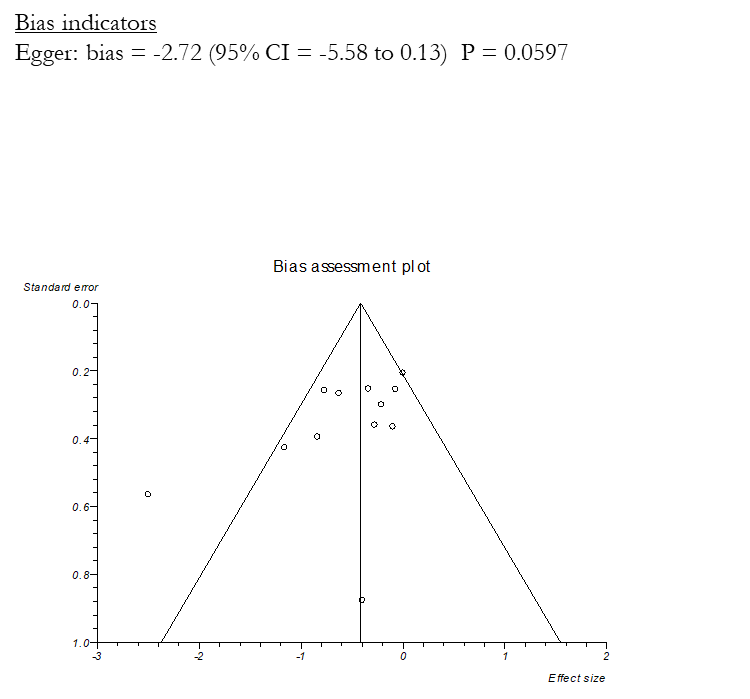
**Isotime inspiratory capacity**

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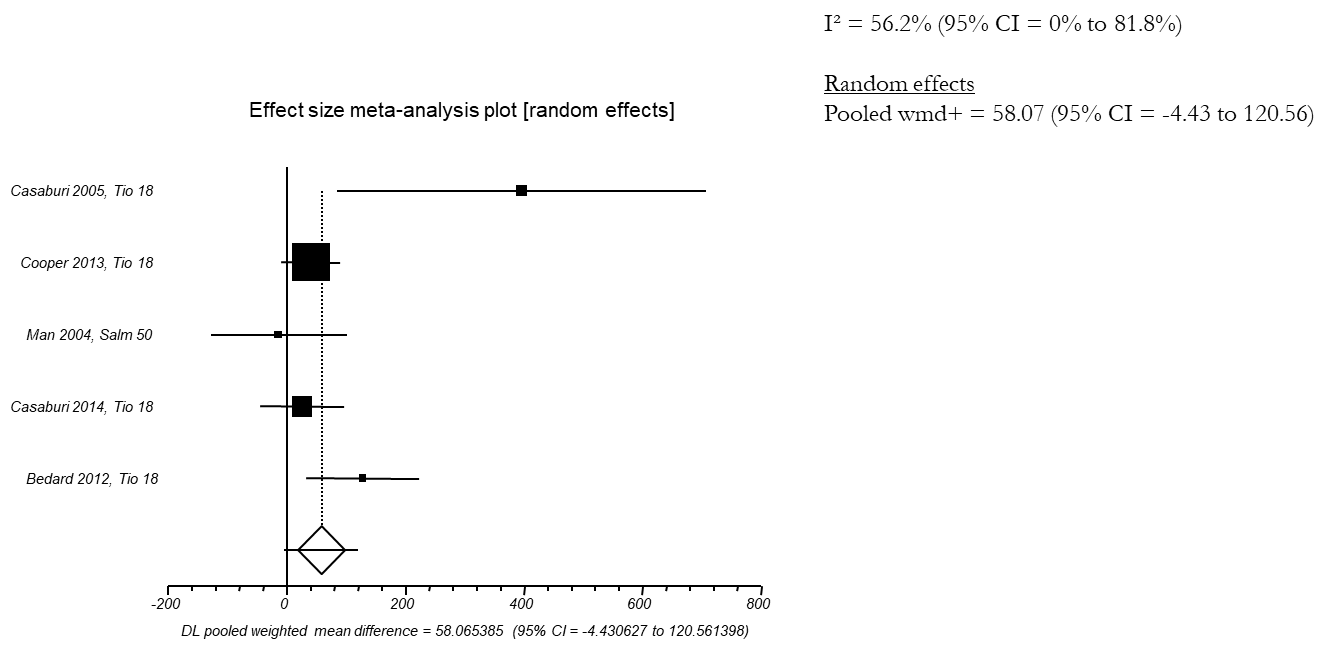
**Isotime dyspnea BORG**

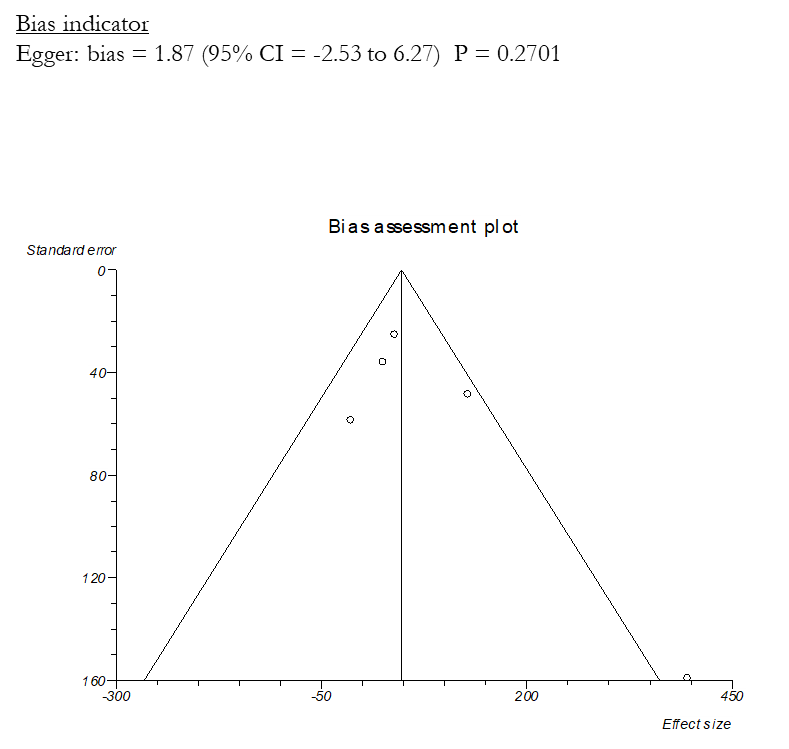
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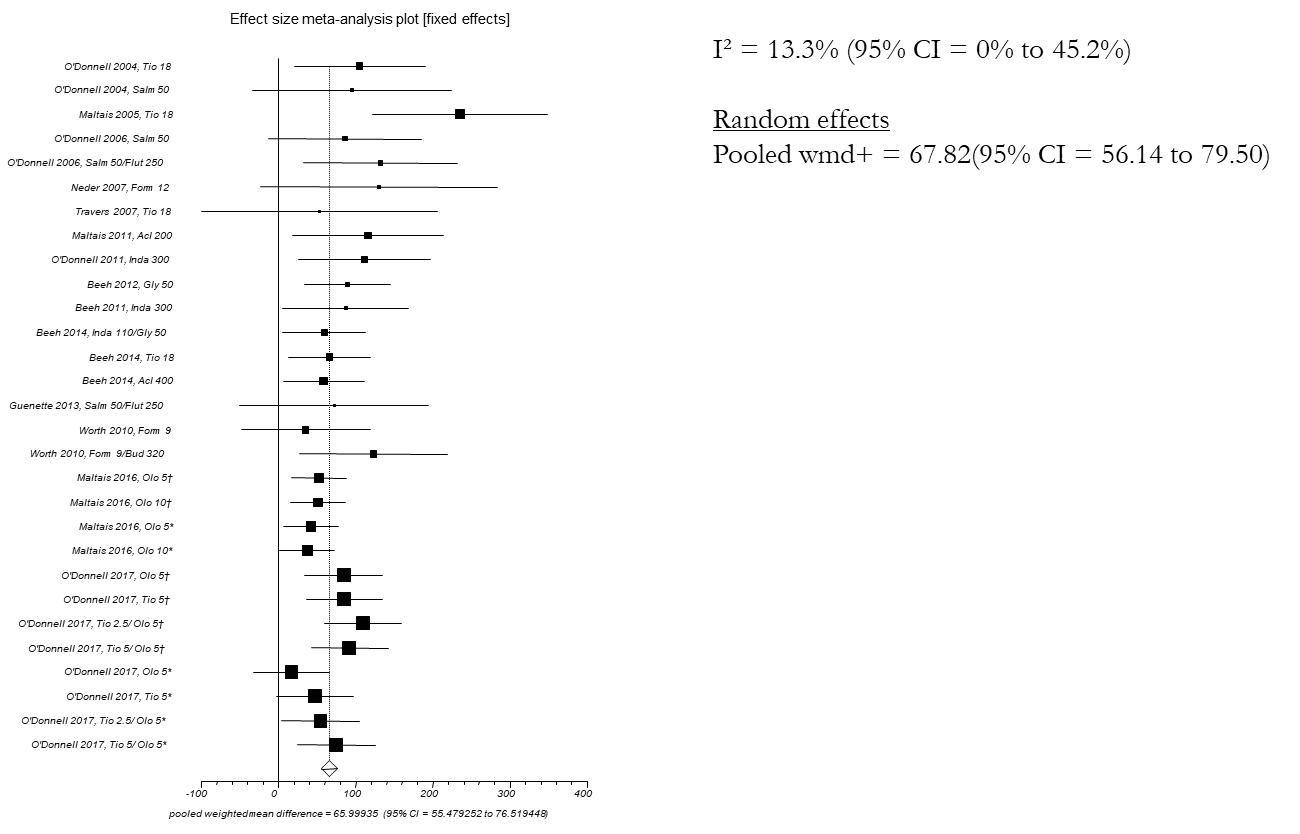
**Figure S3.** Forest and Funnel plots of ET of the 5 studies (A) which used walking and 17 studies (B) which used cycling as exercise methodology to assess the efficacy of long-acting bronchodilators.

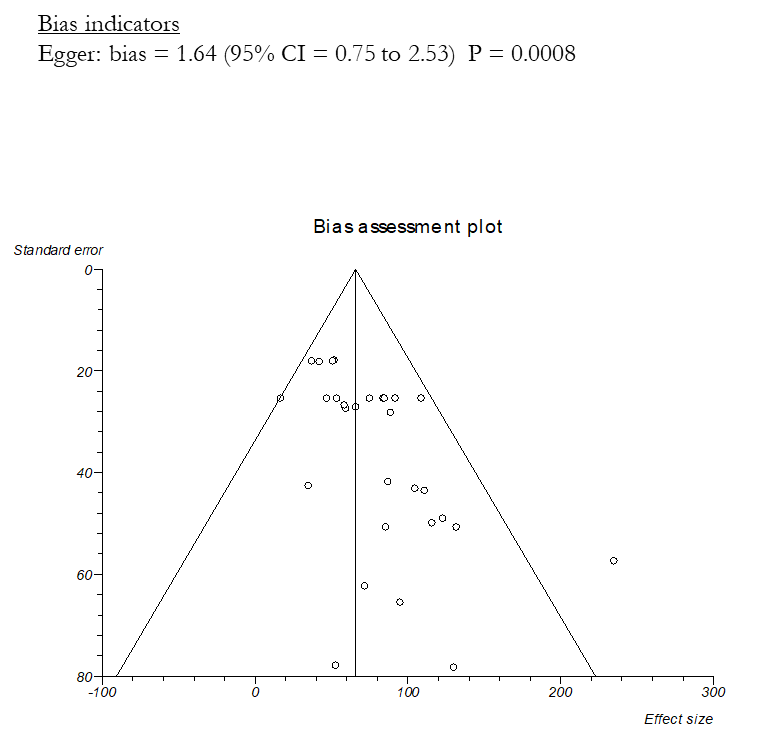
**A)**

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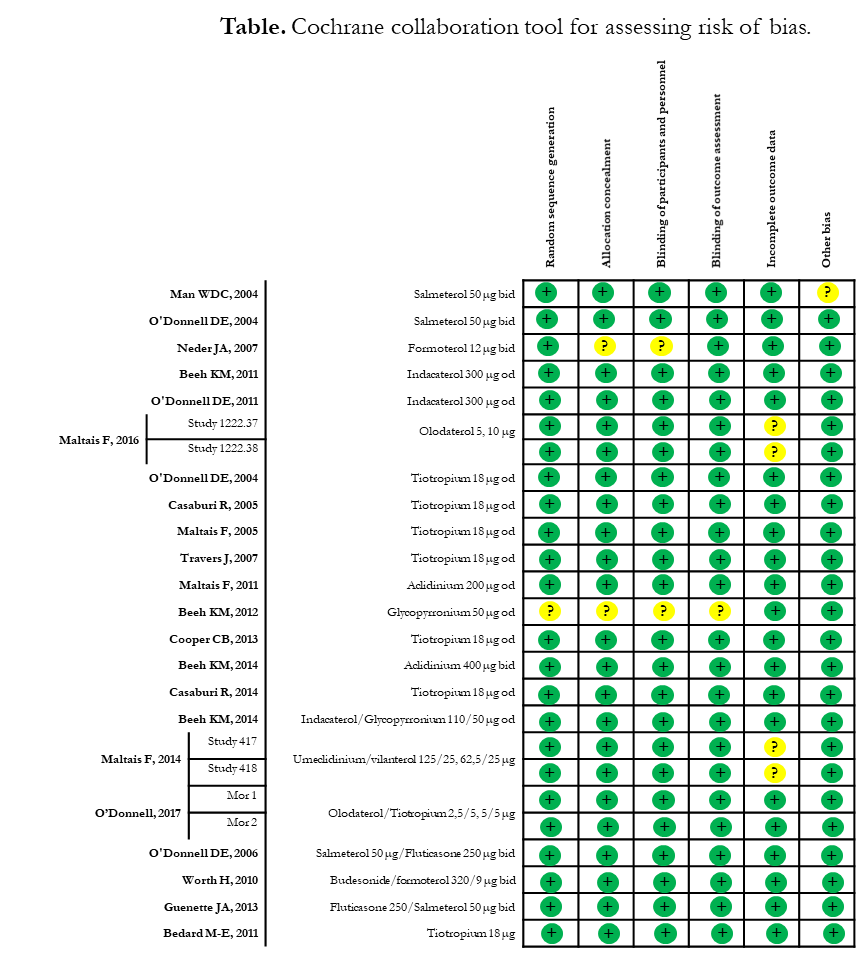
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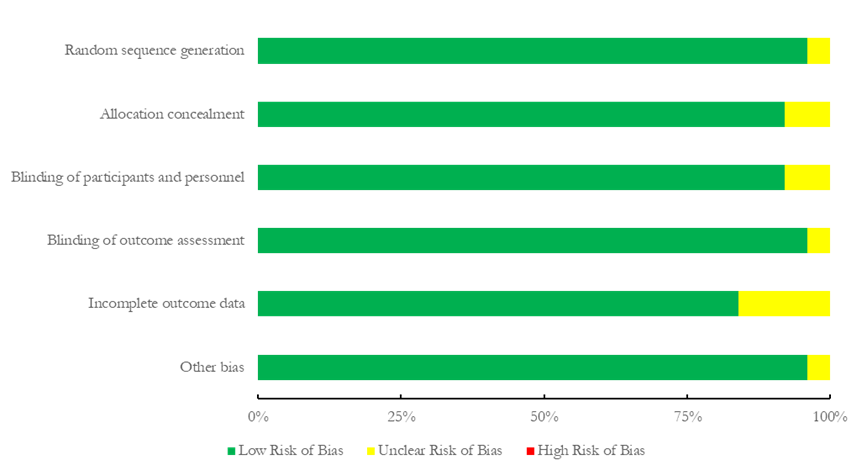
**B)**

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**Table S1.** Cochrane collaboration tool for assessing risk of bias.





**Table S2**. List of and reason why studies on long-acting bronchodilators have been excluded from the analysis.

|  |  |
| --- | --- |
| **Study** | **Reason for exclusion** |
| Canto ND, et al. Addition of tiotropium to formoterol improves inspiratory muscle strength after exercise in COPD. Respir Med 2012; 106: 1404–1412. | No placebo arm |
| Tzani P, et al.[Effects of beclomethasone/formoterol fixed combination on lung hyperinflation and dyspnea in COPD patients.](https://www.ncbi.nlm.nih.gov/pubmed/22069361) Int J Chron Obstruct Pulmon Dis. 2011;6:503-9. | No placebo arm |
| [Berton DC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Berton%20DC%5BAuthor%5D&cauthor=true&cauthor_uid=20580216), et al. Effects of tiotropium and formoterol on dynamic hyperinflation and exercise endurance in COPD. [Respir Med.](https://www.ncbi.nlm.nih.gov/pubmed/20580216) 2010 Sep;104(9):1288-96. | No placebo arm |
| [Magnussen H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Magnussen%20H%5BAuthor%5D&cauthor=true&cauthor_uid=22749044), et al. Effect of combination treatment on lung volumes and exercise endurance time in COPD. [Respir Med.](https://www.ncbi.nlm.nih.gov/pubmed/?term=magnussen+2012+copd+endurance+time) 2012 Oct;106(10):1413-20. | No placebo arm |
| Yoshimura K, et al. Effects of tiotropium on sympathetic activation during exercise in stable chronic obstructive pulmonary disease patients. Int J Chron Obstruct Pulmon Dis 2012; 7: 109–117. | No placebo arm |
| [Brouillard C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Brouillard%20C%5BAuthor%5D&cauthor=true&cauthor_uid=18057052), et al. Endurance shuttle walking test: responsiveness to salmeterol in COPD. [Eur Respir J.](https://www.ncbi.nlm.nih.gov/pubmed/18057052) 2008 Mar;31(3):579-84. | Duration < 1 week |
| [van der Vaart H](https://www.ncbi.nlm.nih.gov/pubmed/?term=van%20der%20Vaart%20H%5BAuthor%5D&cauthor=true&cauthor_uid=21660300), et al. Bronchodilation improves endurance but not muscular efficiency in chronic obstructive pulmonary disease. [Int J Chron Obstruct Pulmon Dis.](https://www.ncbi.nlm.nih.gov/pubmed/?term=van+der+vaart+grevink+postma) 2011;6:229-35. | Data expressed only as difference vs. placebo and not high intensity protocol |
| [Watz H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Watz%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28883722), et al. ACTIVATE: the effect of aclidinium/formoterol on hyperinflation, exercise capacity, and physical activity in patients with COPD. [Int J Chron Obstruct Pulmon Dis.](https://www.ncbi.nlm.nih.gov/pubmed/?term=watz+activate+copd+aclidinium) 2017 Aug 24;12:2545-2558. | Data expressed only as difference vs. placebo |
| [Zhang X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20X%5BAuthor%5D&cauthor=true&cauthor_uid=20040610), et al. Advantages of endurance treadmill walking compared with cycling to assess bronchodilator therapy. [Chest.](https://www.ncbi.nlm.nih.gov/pubmed/?term=zhang+chest+2010+endurance+time+copd) 2010 Jun;137(6):1354-61. | Data expressed only as difference vs. placebo |