Online Data Supplement

Inspiratory Muscle Rehabilitation in Critically Ill Adults: A Systematic Review and Meta-Analysis

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Search Strategy

We employed Medical Subject Headings and keywords for studies of critically ill, mechanically ventilated patients who underwent IMT were used to search all databases: Intensive care units OR intensive care OR critical care OR critical illness OR respiratory insufficiency OR artificial respiration OR positive-pressure respiration OR mechanical ventilation), AND (respiratory muscle training OR inspiratory muscle training OR respiratory muscles OR breathing exercises OR physiotherapy. Proceedings of the American Thoracic Society and European Society of Intensive Care Medicine conferences from 2011-2017 were reviewed for potential studies of interest. We also searched the bibliographies of included studies and review articles.

Statistical Analysis

Mean changes in variables from pre- to post-treatment were computed by subtraction; the standard deviation (SD) of the change was estimated by

$\sqrt{SD_{pre-IMT}{}^2 + SD_{post-IMT}{}^2 + 2 \cdot SD_{pre-IMT} \cdot SD_{post-IMT}}$ where ρ is the assumed correlation between pre- and post-treatment values (assumed to be 0.8 in our analysis, as this gave computed values that closely match actual values for studies that reported the actual standard deviation of the change).

The logarithm of the ratio of means (mean post-treatment MIP:mean pre-treatment MIP) was computed for each arm of each study. The variance of the logarithm of ratio of means was computed as:

$$\frac{1}{n_{post}}\left(\frac{sd_{post}}{mean_{post}}\right)^2 + \frac{1}{n_{pre}}\left(\frac{sd_{pre}}{mean_{pre}}\right)^2 + 2 \cdot \rho \cdot \left(\sqrt{\frac{1}{n_{post}}\left(\frac{sd_{post}}{mean_{post}}\right)^2}\right) \cdot \left(\sqrt{\frac{1}{n_{pre}}\left(\frac{sd_{pre}}{mean_{pre}}\right)^2}\right)$$

according to a previously reported technique (1). Again, ρ was assumed to be 0.8. These ratio of means values were pooled by computing the difference in the log(ratio of means) between IMT and control. The variance of this difference was computed by adding the variance of the logarithm of the ratio of means for the experimental and control groups. Effects were pooled across studies using the generic inverse variance method [1].

Table E1. Characteristics of studies of inspiratory muscle training in critically ill patients

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Bissett et al. 2016 (2)	Evaluate the impact of IMT on recovery after acute respiratory failure requiring mechanical ventilation	Single-center RCT	Patients who were successfully liberated from the ventilator (48 hours to 7 days post-extubation) after ≥7 days of invasive mechanical ventilation	70	Threshold loading (threshold IMT device, Respironics) initiated at 50% of $P_{i,max}$ then increased to highest tolerable intensity (five sets of six breaths per session) conducted daily for 2 weeks Control: no IMT	IMT initiated after extubation and applied for 2 weeks
Cader et al. 2010 (3)	Evaluate effect of IMT on $P_{i,max}$	Single-center RCT	Patients aged ≥ 70 years on mechanical ventilation for ≥ 48 hours	28	Threshold loading (threshold IMT device) commenced at 30% of $P_{i,max}$, increased by 10% per day as tolerated, applied for 5 minutes twice per day Control: no IMT	IMT was applied at the start of weaning until extubation
Caruso et al. 2005 (4)	Evaluate the effect of IMT from onset of MV on duration of weaning and reintubation rate	Single-center RCT	Patients predicted to required invasive mechanical ventilation for ≥ 72 hours	40	Threshold loading (ventilator pressure trigger set to 20% of $P_{i,max}$) applied for 5 minutes, progressively prolonged to 30 minutes, then load increased by 10% of $P_{i,max}$ Control: no IMT	IMT was applied 24 hours after starting mechanical ventilation until extubation
Chang et al. 2011 (5)	Evaluate the effect of sitting in a chair during exercise training on $P_{i,max}$	Single-center RCT	Patients on mechanical ventilation for ≥ 72 hours	34	Transferred from bed to sit in chair for 30-120 minutes as tolerated Control: no physical therapy	6 days

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Condessa et al. 2013 (6)	Evaluate the effect of IMT on duration of weaning from mechanical ventilation	Single-center RCT	Adults receiving mechanical ventilation for > 48 hours meeting readiness-to-wean criteria	92	Threshold loading (threshold IMT device) at 40% of MIP; 5 sets of 10 breaths performed twice daily Control: no IMT	IMT was applied until extubation, tracheostomy, death, or resumption of controlled ventilation
Dixit et al. 2014 (7)	Evaluate the effect of IMT on duration of weaning from mechanical ventilation	Single-center RCT	Adults receiving mechanical ventilation > 24 hours meeting readiness-to-wean criteria	30	Threshold loading (threshold IMT device) at 30% of $P_{i,max}$, adjusted to patient tolerance, increased daily by 10% of $P_{i,max}$; 5 sets of 6 breaths performed twice daily Control: no IMT	IMT was applied 7 days per week until extubation
Holliday et al. 1990 (8)	Evaluate the effect of respiratory pattern biofeedback on duration of weaning from mechanical ventilation	Single-center RCT	Patients receiving mechanical ventilation for ≥ 7 days	40	Biofeedback-guided deep breathing exercises via respiratory inductance plethysmography for 30-50 minutes per day Control: usual care	IMT was applied at the start of weaning for 5 days per week until weaned from ventilator support
Ibrahiem et al. 2014 (9)	Evaluate the effect of IMT in mechanically ventilated patients	Single-center RCT	Adults receiving mechanical ventilation for at least 3-7 days who meet readiness-to-wean criteria	30	Threshold loading (threshold IMT device) at 20% of $P_{i,max}$ (increased by 1-2 cm H_2O per day); 5 sets of 6 breaths twice daily Control: no IMT	3 days

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Martin AD et al. 2011 (10)	Evaluate the effect of IMT on weaning from mechanical ventilation	Single-center RCT	Patients with difficult weaning from mechanical ventilation (≥72 hours of weaning)	69	Threshold loading (threshold IMT device) applied at the highest tolerable pressure threshold; 4 sets of 6-10 breaths per day (2 minutes of rest on ventilation between sets) Control: sham IMT	IMT was applied until weaned from ventilator support or for 28 days
Melo et al. 2017 (11)	Elucidate the effect of IMT on patients with traumatic brain injuries (TBI) undergoing mechanical ventilation	Single-center RCT	TBI patients receiving mechanical ventilation for more than 7 days	10	Threshold loading device (threshold IMT device), at 50% of daily MIP. Control: usual care	IMT was applied for 2 weeks
Mohamed et al. 2014 (12)	Evaluate the effect of IMT on respiratory muscle strength	Single-center RCT	Patients requiring invasive mechanical ventilation for ≥ 48 hours meeting readiness-to-wean criteria	40	Threshold loading (threshold IMT device) initially applied at 30% of $P_{i,max}$, 5-6 sets of 6 breaths, twice daily; increased by 1-2 cm H_2O daily as tolerated Control: no IMT	7 days

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Nava et al. 1998 (13)	Evaluate the physiological effects of pulmonary rehabilitation after acute respiratory failure	Single-center RCT	COPD patients recovering from acute respiratory failure (76% receiving ventilator support at enrolment)	80	Postural training, early ambulation, IMT by threshold loading (threshold IMT device) applied at 50% of $P_{i,max}$ for 10 minutes twice daily, cycling, stair climbing, treadmill training Control: no IMT	Not specified
Özyürek et al. 2014 (14)	Evaluate the effect of post-operative IMT on respiratory muscle strength after upper abdominal surgery	Single-center RCT	Patients undergoing upper abdominal surgery	40	IMT commenced on day of extubation. Threshold loading (threshold IMT device) initially applied at 30% of MIP for 15 minutes daily, pressure titrated up by 2 cm H_2O per day as tolerated based on exertion score Control: no IMT	IMT was applied until hospital discharge
Pascotini et al. 2014 (15)	Evaluate the effect of respiratory muscle training on respiratory muscle strength in patients weaning from ventilation	Single-center RCT	Patients ≥ 40 years of age with tracheostomy undergoing weaning from ventilation	14	Threshold loading (threshold IMT device) applied at 20% of $P_{i,max}$ for 3 sets of 10 breaths once daily. Control: no IMT	7 days

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Porta et al. 2005 (16)	To evaluate the feasibility of upper extremity exercise training added to general physiotherapy	Multi-center RCT	Patients successfully weaned after prolonged mechanically ventilation	66	Upper-arm cycling on the arm ergometer: Incremental tests (IT): 1-minute exercise, followed by 1-minute unloaded cycling at 40-45 cycles/minute then increase the load by 2.5W/min until reach exhaustion Endurance test: 50% of peak work rate reached on IT cycling at 40-45 cycles/minute until exhaustion Control: no upper extremity exercise	15 days
Saad et al. 2014 (17)	Evaluate the effect of employing an IMT device on respiratory muscle strength	Single-center RCT	Difficult-to-wean patients with a tracheostomy	25	Threshold loading (threshold IMT device) initially applied at 30% of initial $P_{i,max}$, increasing by 10% daily; 3 sets of 10 cycles once daily Control: no IMT	Not specified
Shimizu et al. 2014 (18)	Evaluate the effect of IMT on weaning outcome (secondary objective)	Single-center RCT	Patients receiving invasive mechanical ventilation for ≥ 48 hours who fail a SBT	13	Threshold loading (threshold IMT device) applied at 50% of $P_{i,max}$ for 3 sets of 10 breaths, twice daily Control: no IMT	4 days

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Shrestha et al. 2014 (19)	Explore the feasibility and safety of using IMT to exercise the respiratory muscles in critically ill intubated patients	Single-center RCT	Mechanically ventilated patients who failed a 2-hour spontaneous breathing trial (lasting at least 5 minutes)	7	Threshold loading (threshold IMT device), protocol not otherwise specified Control: sham IMT	Not specified
Tonella et al. 2017 (20)	Compare effects of electronic IMT (eIMT) with an intermittent nebulization program (INP)	Single-center RCT	Tracheostomized patients meeting readiness-to-wean criteria	19	Threshold loading (threshold IMT device), at 30% of initial MIP, increasing by 10% daily; 3 sets of 10 breaths conducted twice daily Control: INP through a T-piece until weaned	IMT and INP applied until weaned from ventilator support
Yosef-Brauner et al. 2015 (21)	Evaluate the effect of an intensive physical therapy protocol in patients with ICU-acquired weakness	Single-center RCT	Patients on mechanical ventilation for ≥ 48 hours and anticipated to require additional ≥48 hours	18	Passive and active range-of-motion exercise, breathing exercises (not otherwise specified), trunk exercise, manual hyperinflation, ambulation Control: no IMT	Physical therapy was applied until ICU discharge

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Aldrich et al. 1989 (22)	Improve respiratory muscle endurance by IMT	Single-group observational study	MV duration ≥ 3 weeks and repeated failed T-piece trials	30	Applied inspiratory resistance (starting at 8 cm H_2O/L/sec at 0.25 L/sec) for 5-10 minutes and progressively increased duration (maximum of 30 minutes) and resistance level.	IMT applied for at least 2 weeks until weaned from ventilator support or treatment failure (no improvement in MIP).
Barros et al. 2015 (23)	Evaluate the effect of standardized mobilization protocol on respiratory muscle strength in mechanically ventilated patients	Single-group observational trial	Mechanically ventilated patients	10	5-phase mobilization strategy (progression from passive mobilization to walking)	Not specified
Chiang et al. 2006 (24)	Evaluate the effect of physical therapy (PT) on respiratory and limb muscle strength	Single-center observational study with control comparison	Patients on mechanical ventilation for > 14 days	39	Upper and lower extremity strengthening exercises and diaphragmatic breathing exercises Control: no PT	IMT was applied 5 times per week for 6 weeks

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Elbouhy et al. 2014 (25)	Evaluate the effect of IMT on duration of weaning from mechanical ventilation in COPD patients	Single-center observational study with control comparison	Patients with prolonged weaning from mechanical ventilation after acute exacerbations of COPD	40	Threshold loading (PSV 8 cm H_2O, ventilator pressure trigger set at 20% of $P_{i,max}$) applied for 5 minutes; duration progressively increased to 30 minutes, then threshold load increased by 10% of $P_{i,max}$ Control: no IMT	IMT was applied for 5 days
Martin AD et al. 2002 (26)	Evaluate the effect of IMT on weaning from mechanical ventilation	Case series	Patients with prolonged weaning from mechanical ventilation (≥7 days of weaning)	10	Threshold loading (threshold IMT device) adjusted to exertion level; 3-5 sets of 6 breaths once daily	IMT was applied 5-7 days per week until weaned from ventilator support
Martin UJ et al. 2005 (27)	Evaluate the effect of physical therapy on weaning from mechanical ventilation and respiratory muscle strength	Retrospective cohort	Patients with prolonged mechanical ventilation ≥ 14 days, failed at least 2 weaning attempts	49	Comprehensive physical therapy program including IMT by threshold loading (threshold IMT device) at 1/3 of $P_{i,max}$ for 15 minutes twice daily	IMT was applied until weaned from ventilator support
Sprague et al. 2003 (28)	Describe the rationale and application of IMT in difficult weaning from ventilation	Case series	Mechanically ventilated patients requiring prolonged weaning	6	Threshold loading (threshold IMT device), at approximately 50% of $P_{i,max}$; 4 sets of 6-8 breaths conducted daily	IMT was applied until ICU discharge

Reference	Objectives	Study Design	Population	N	Intervention and Control	Timing & Duration
Supinski et al. 2017 (29)	Determine physical therapy (PT) would improve inspiratory muscle strength and lung function	Single-center observational study	Mechanically ventilated patients	22	PT	PT was applied for 2 weeks

Table E2. Methodological quality of observational studies using the Newcastle Ottawa Scale

Study	Selection	Comparability	Outcome
Aldrich 1989	*		***
Barros 2015	*		
Chiang 2006	***		***
Elbouhy 2014	***	*	***
Martin 2002	*		***
Martin 2005	*		***
Sprague 2003	*		***
Supinski 2017	*		

A study can be awarded a maximum of four stars in the Selection category, a maximum of two stars can be given for Comparability, a maximum of three starts in the Outcome category. The number of stars indicates the methodologic quality of the study. Fewer stars corresponds with lower quality.

Table E3. Methodological Characteristics of Maximal Inspiratory Pressure Measurement

Study	Quality Marker			
	Coaching	One-way valve	Patient awake and co-operative	MIP Assessor Blinded to Randomization
Aldrich 1989	Yes	No	Yes	-*
Barros 2015	-	-	-	-
Bissett 2016	Yes	-	Yes	Yes
Cader 2010	No	Yes	-	No
Caruso 2005	-	Yes	-	-
Chang 2011	-	-	-	-
Chiang 2006	Yes	-	Yes	Yes
Condessa 2013	Yes	Yes	Yes	No
Dixit 2014	-	-	-	-
Elbouhy 2014	-	-	-	-
Holliday 1990	-	-	-	-
Ibrahiem 2014	-	No	Yes	-
Martin 2002	-	-	-	-
Martin 2005	-	-	-	-
Martin 2011	Yes	Yes	Yes	No
Melo 2017	-	-	-	Yes
Mohamed 2014	-	-	-	-
Nava 1998	Yes	Yes	Yes	-
Özyürek 2014	-	-	-	-
Pascotini 2014	Yes	Yes	Yes	No
Porta 2005	-	-	-	-
Saad 2014	-	Yes	-	-
Shimizu 2014	No	Yes	-	No
Shrestha 2014	-	-	-	-
Sprague 2003	Yes	-	Yes	-
Tonella 2017	No	Yes	-	No
Yosef-Brauner 2015	-	-	-	Yes

*Hyphen = not reported

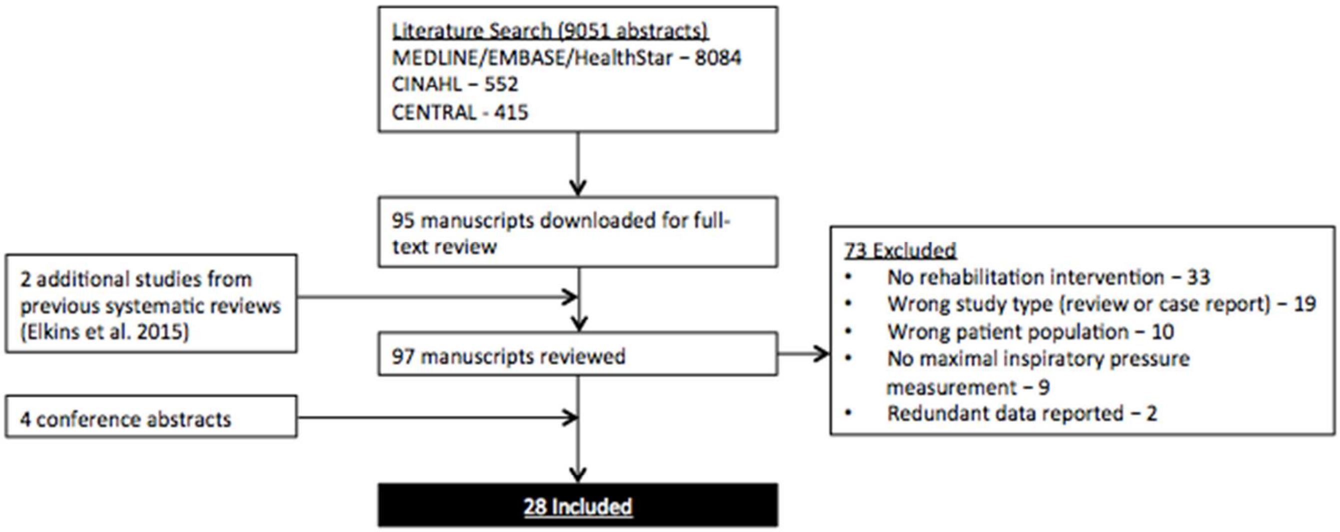

Figure E1. Study selection process for the systematic review.

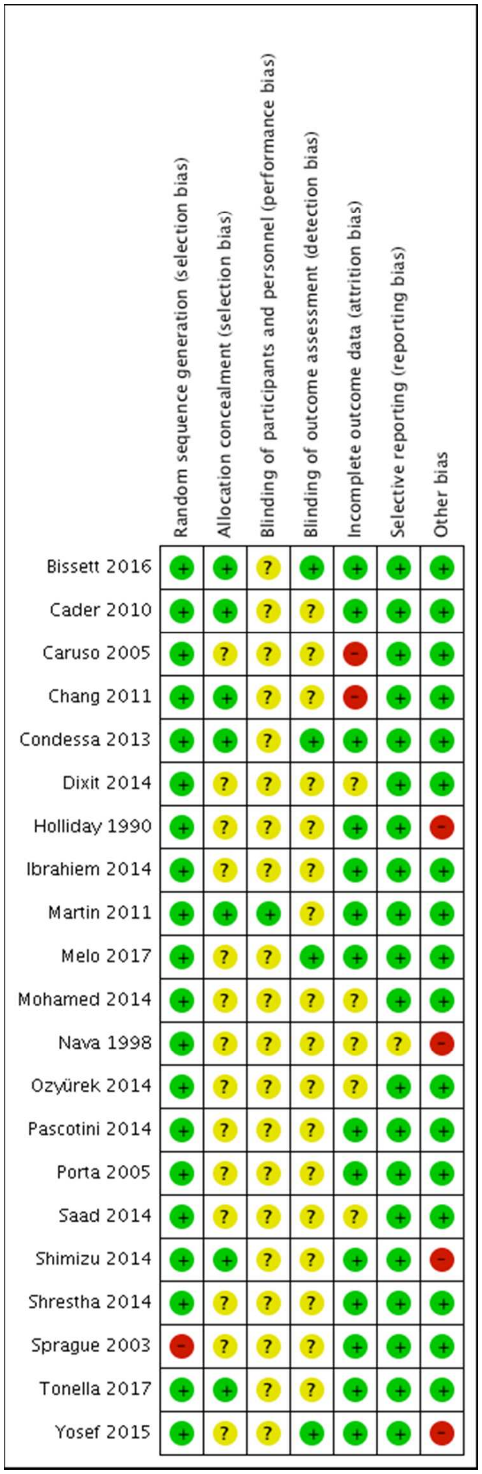

Figure E2. Risk of bias in randomized controlled trials. Red circles indicate serious risk of bias on the evaluated factor, green circles indicate low risk of bias, and yellow circles indicate uncertain risk of bias. Lack of blinding was deemed to result in an unclear bias (see text for details). “Other bias” refers to the use of co-interventions.

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight
Pascotini 2014	7	0.23	0.54	7	-0.22	0.22	0.45	[0.02; 0.88]	1.0%
Cader 2010	14	0.51	0.09	14	0.18	0.06	0.33	[0.27; 0.39]	8.9%
Condessa 2013	45	0.19	0.10	47	-0.08	0.08	0.27	[0.23; 0.31]	9.7%
Özyürek 2014	15	1.04	0.08	16	0.81	0.18	0.23	[0.13; 0.33]	7.0%
Mohamed 2014	20	0.32	0.05	20	0.10	0.03	0.22	[0.19; 0.25]	10.1%
Ibrahiem 2014	15	0.27	0.05	15	0.06	0.09	0.21	[0.16; 0.26]	9.1%
Dixit 2014	15	0.42	0.08	15	0.22	0.05	0.20	[0.15; 0.25]	9.3%
Bissett 2016	33	0.34	0.19	36	0.16	0.18	0.18	[0.09; 0.27]	7.4%
Martin 2011	35	0.20	0.12	34	0.02	0.14	0.18	[0.12; 0.24]	8.7%
Holliday 1990	20	0.33	0.04	16	0.19	0.04	0.14	[0.11; 0.17]	10.1%
Porta 2005	32	0.19	0.14	34	0.13	0.12	0.06	[0.00; 0.12]	8.6%
Caruso 2005	12	0.09	0.15	13	0.14	0.23	-0.05	[-0.20; 0.10]	4.7%
Tonella 2017	11	0.12	0.19	8	0.21	0.25	-0.09	[-0.30; 0.12]	3.2%
Chang 2011	8	0.29	0.24	5	0.49	0.42	-0.20	[-0.60; 0.20]	1.1%
Shimizu 2014	8	-0.16	0.22	5	0.06	0.45	-0.22	[-0.64; 0.20]	1.0%
Random effects model	**290**			**285**			**0.17**	**[0.13; 0.22]**	**100.0%**

Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.0049$, $p < 0.01$

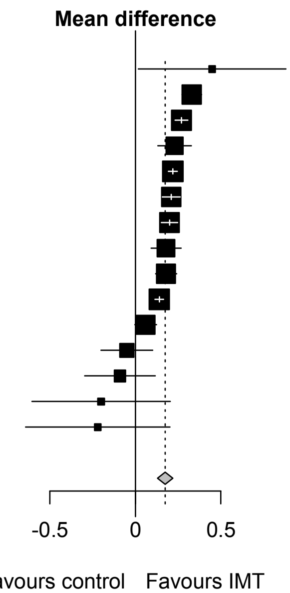

Figure E3. Pooled effect of IMT on MIP relative to baseline compared to controls. For this analysis, the difference in the logarithm of the ratio of post-treatment MIP to pre-treatment MIP between IMT and control (and the variance of this difference) for each study were pooled using the generic inverse variance method. Pooled effects were back transformed to obtain the estimate effect (pooled relative ratio of means 1.19 [95% CI 1.14-1.25]).

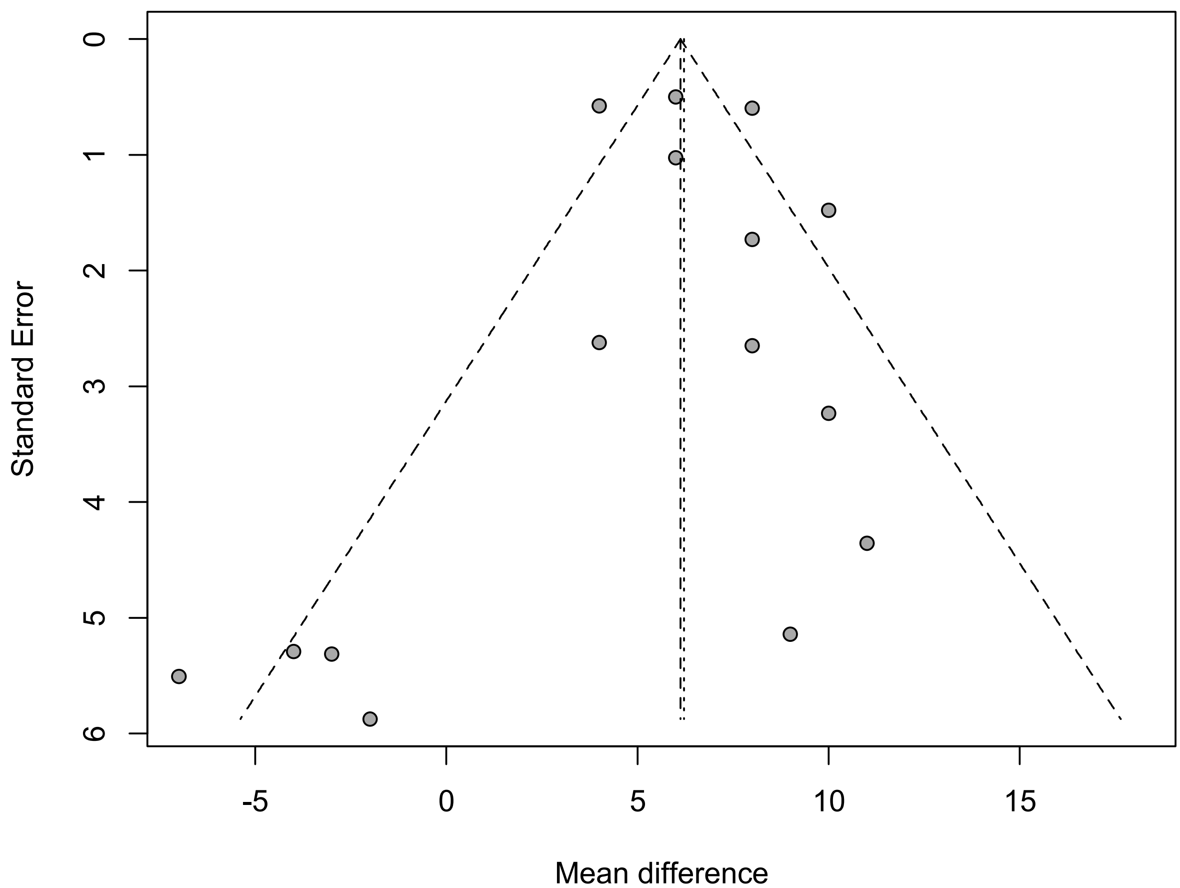

Figure E4. Funnel plot assessing for publication bias in primary end-point. No evidence of publication bias was detected (p=0.73 for test of asymmetry by linear regression of treatment effect against standard error (30)).

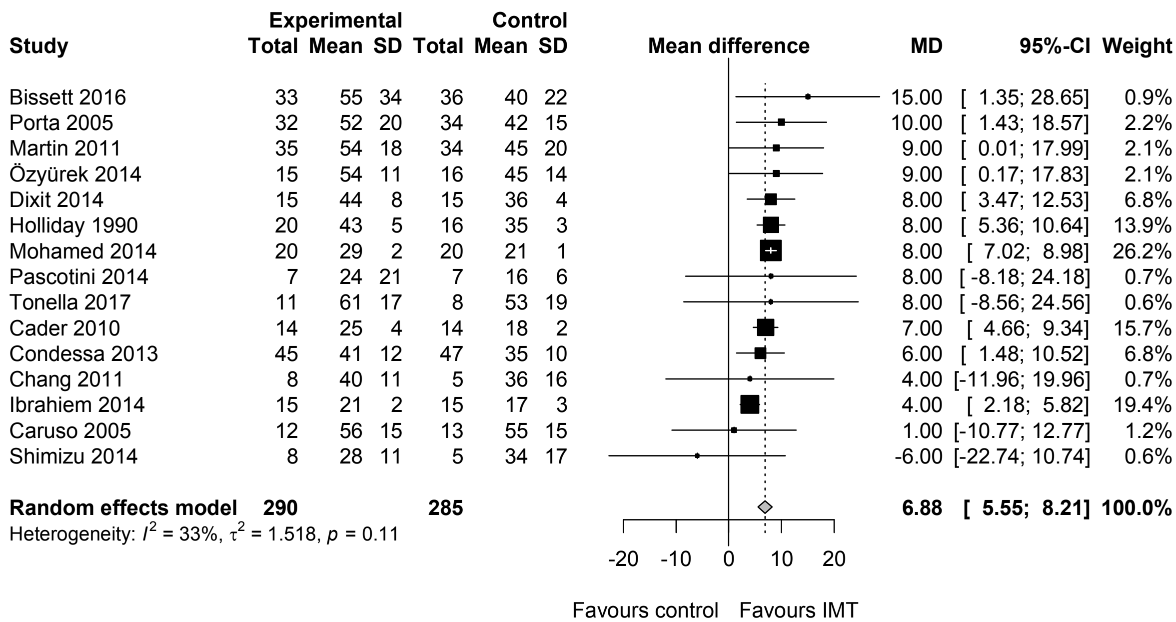

Figure E5. Effect of inspiratory muscle training on maximal inspiratory pressure at the completion of treatment course.

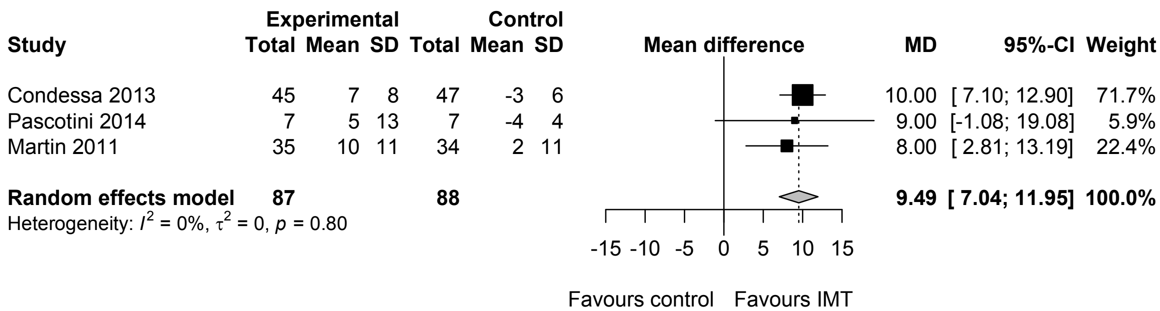

Figure E6. Sensitivity analysis of pooled effect of inspiratory muscle training on the increase in MIP from baseline in studies without high risk of bias that employed rigorous technique for measurement of MIP.

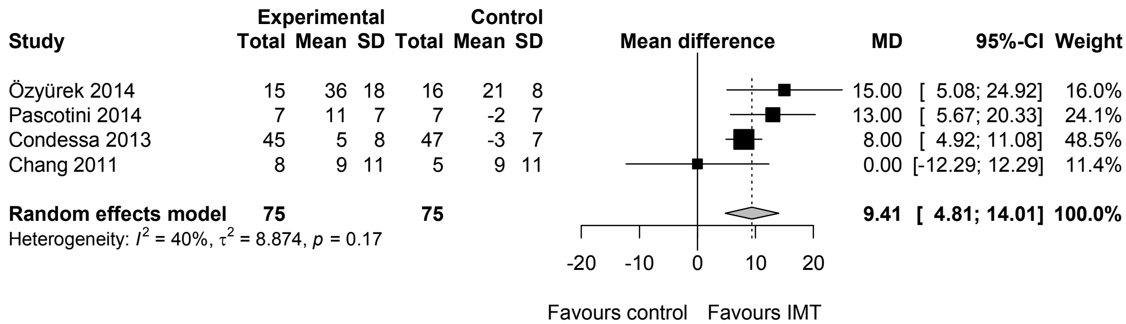

Figure E7. Impact of inspiratory muscle training on maximal expiratory pressure (MEP).

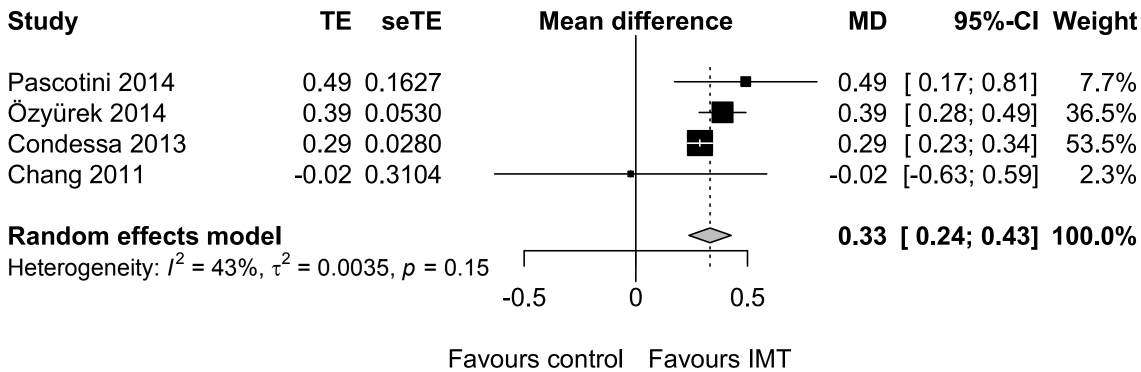

Figure E8. Pooled effect of IMT on maximal expiratory pressure (MEP) relative to baseline MEP compared to controls. For this analysis, the difference in the logarithm of the ratio of post-treatment MEP to pre-treatment MEP between IMT and control (and the variance of this difference) for each study were pooled using the generic inverse variance method. Pooled effects were back transformed to obtain the estimate effect (pooled relative ratio of means 1.39 [95% CI 1.27-1.54]).

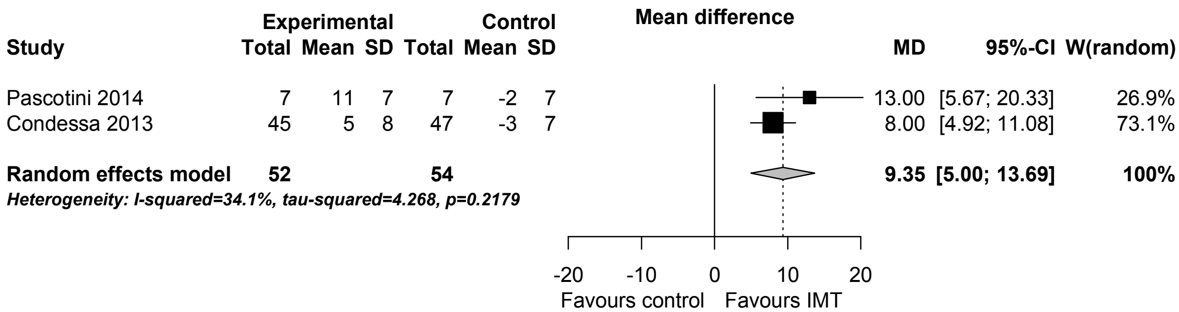

Figure E9. Sensitivity analysis of studies examining the impact of inspiratory muscle training on maximal expiratory pressure. For this analysis, studies at high risk of bias were excluded.

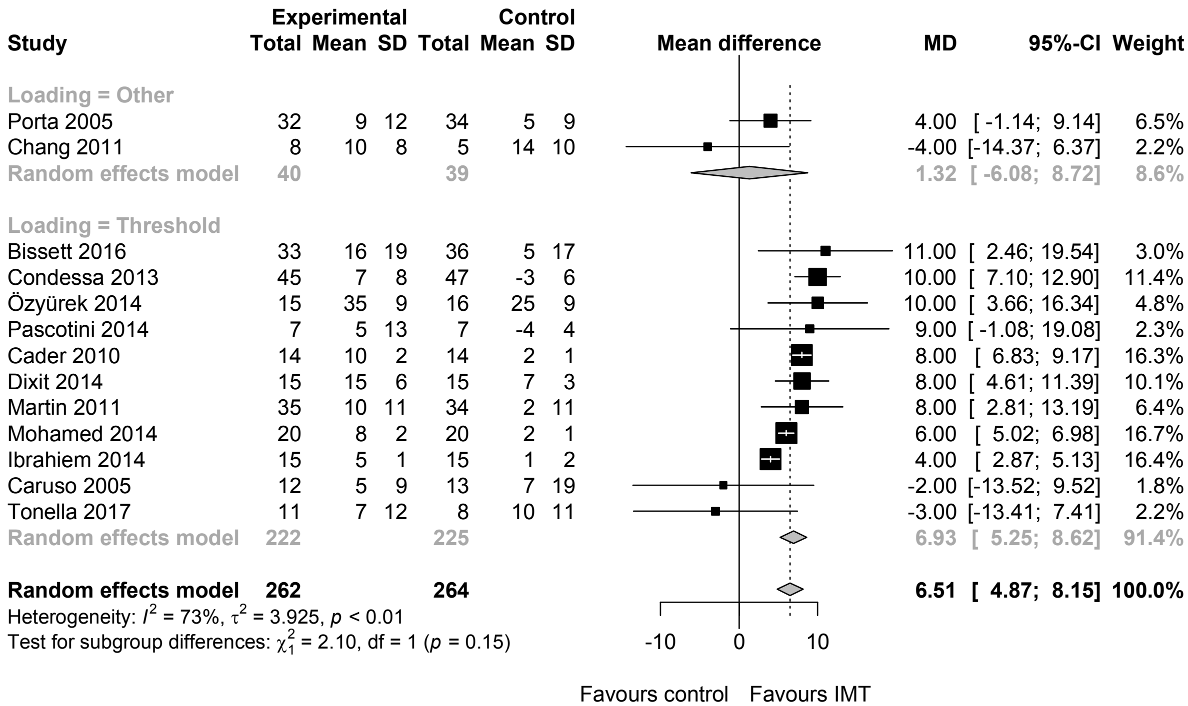

Figure E10. Comparative effect of threshold loading-based IMT regimen vs. other IMT regimen on respiratory muscle strength. Threshold loading was associated with significantly greater improvement in respiratory muscle strength.

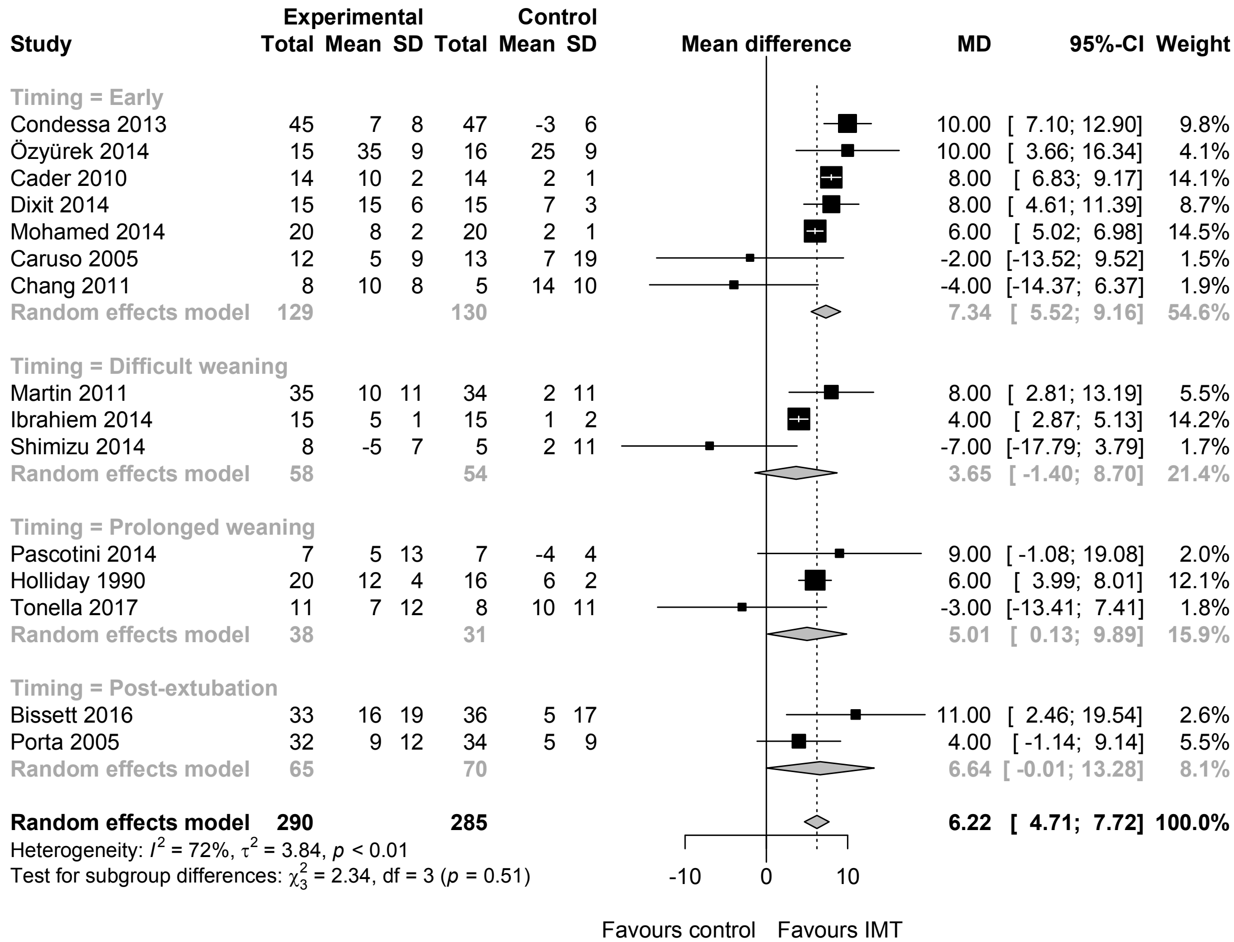

Figure E11. Effect of IMT on respiratory muscle strength when initiated at different time points in the course of critical illness and acute respiratory failure.

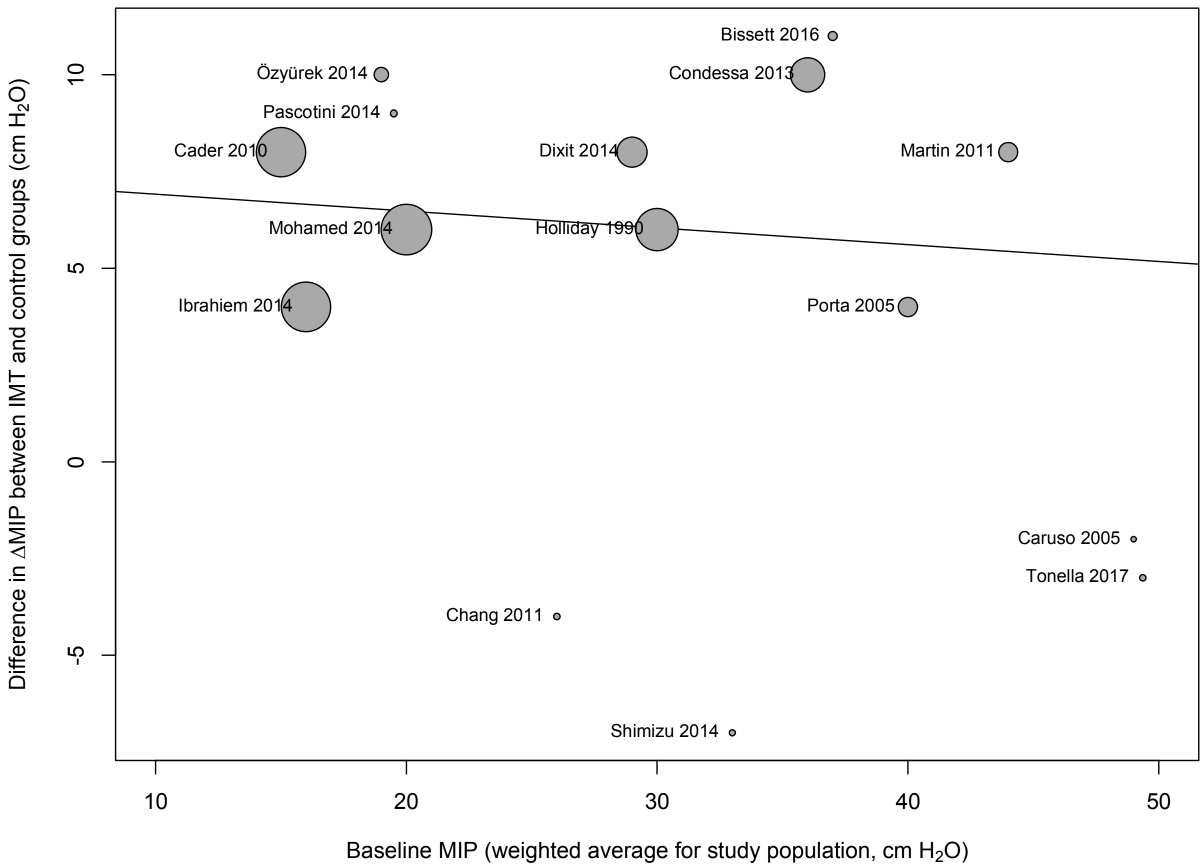

Figure E12. Relationship between pre-treatment maximal inspiratory pressure and treatment effect (increase in MIP from baseline). Treatment effect did not vary with baseline MIP (R^2=0%, p=0.11).

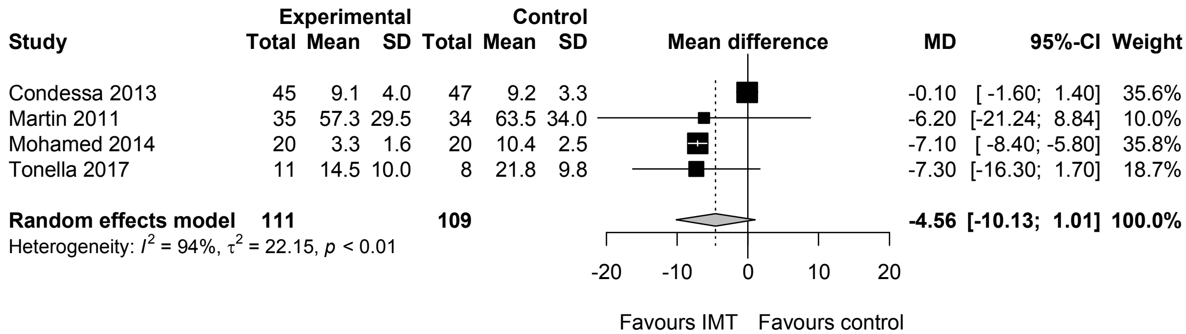

Figure E13. Sensitivity analysis of pooled effect of inspiratory muscle training on duration of mechanical ventilation in studies without serious risk of bias.

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight
Condessa 2013	45	2.2	1.8	47	2.5	2.5	-0.30	[-1.19; 0.59]	22.1%
Cader 2010	14	3.6	1.5	14	5.3	1.9	-1.70	[-2.97; -0.43]	21.5%
Dixit 2014	15	4.3	1.5	15	6.3	1.7	-2.00	[-3.15; -0.85]	21.7%
Tonella 2017	11	3.5	1.6	8	9.4	6.5	-5.90	[-10.50; -1.30]	13.2%
Mohamed 2014	20	3.3	1.6	20	10.4	2.5	-7.10	[-8.40; -5.80]	21.5%
Random effects model	**105**			**104**			**-3.17**	**[-5.77; -0.58]**	**100.0%**

Heterogeneity: $I^2 = 95\%$, $\tau^2 = 7.731$, $p < 0.01$

Test for overall effect: $z = -2.39$ ($p = 0.02$)

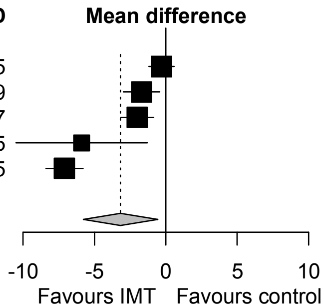

Figure E14. Impact of inspiratory muscle training on the duration of weaning in studies without serious risk of bias.

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight
Melo 2017	6	14	2.5	4	15.0	3.1	-1.00	[-4.64; 2.64]	49.9%
Yosef-Brauner 2015	9	13	4.6	9	18.1	3.1	-5.10	[-8.72; -1.48]	50.1%
Random effects model	**15**			**13**			**-3.05**	**[-7.07; 0.96]**	**100.0%**

Heterogeneity: $I^2 = 59\%$, $\tau^2 = 4.973$, $p = 0.12$

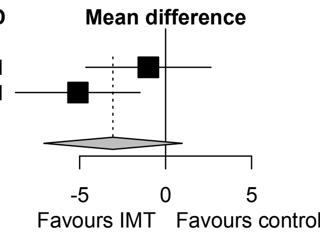

Figure E15. Impact of inspiratory muscle training on ICU length-of-stay.

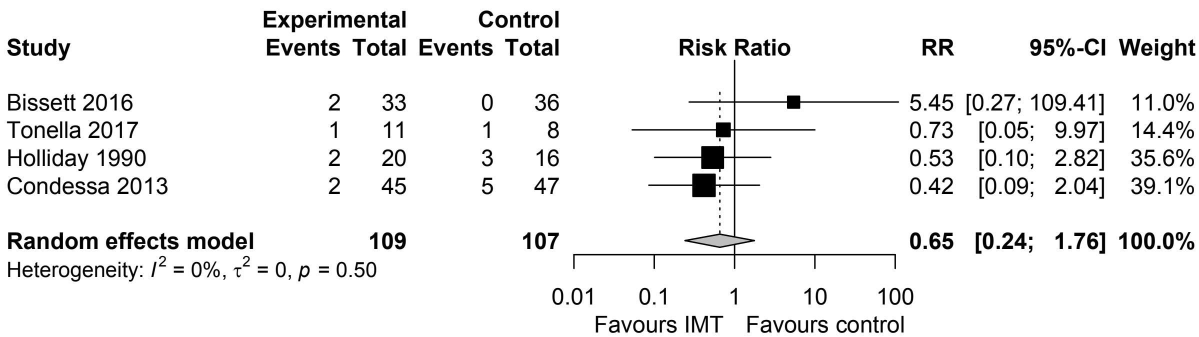

Figure E16. Impact of inspiratory muscle training on the risk of death in the intensive care unit.

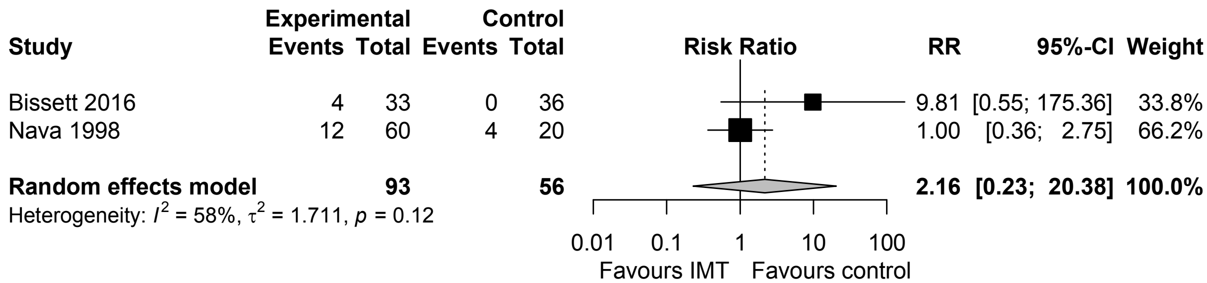

Figure E17. Impact of inspiratory muscle training on the risk of death in hospital.

References

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