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Abdominal functional electrical stimulation to improve respiratory function after spinal cord injury: a systematic review and meta-analysis

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## Abstract

**Background:** Abdominal Functional Electrical Stimulation (Abdominal FES) is the application of a train of electrical pulses to the abdominal muscles, causing them to contract. Abdominal FES has been used as a neuroprosthesis to acutely augment respiratory function and as a rehabilitation tool to achieve a chronic increase in respiratory function after Abdominal FES training, primarily focusing on patients with Spinal Cord Injury (SCI).

**Objective:** This study aimed to review the evidence surrounding the use of Abdominal FES to improve respiratory function in both an acute and chronic manner after spinal cord injury.

**Methods:** A systematic search was performed on PubMed, with studies included if they applied Abdominal FES to improve respiratory function in patients with SCI.

**Results:** Fourteen studies met the inclusion criteria (10 acute, 4 chronic). Low participant numbers and heterogeneity across studies reduced the power of the meta-analysis. Despite this, Abdominal FES was found to cause a significant acute improvement in Cough Peak Flow, while Forced Exhaled Volume in one second approached significance. A significant chronic increase in unassisted Vital Capacity, Forced Vital Capacity and Peak Expiratory Flow was found after Abdominal FES training compared to baseline.

**Conclusions:** This systematic review suggests that Abdominal FES is an effective technique for improving respiratory function in both an acute and chronic manner after SCI. However, further Randomised Controlled Trials, with larger participant numbers and standardised protocols, are needed to fully establish the clinical efficacy of this technique.

## Introduction

Functional Electrical Stimulation (FES) is the application of a train of electrical pulses to a motor nerve, causing the associated muscle to contract.<sup>1</sup> The application of FES to the abdominal muscles is called Abdominal Functional Electrical Stimulation (Abdominal FES). For patients with impaired ventilatory respiration, for example due to paralysis affecting the major

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respiratory muscles, Abdominal FES can be used to activate paralysed abdominal muscles, which may achieve an acute (immediate and temporary) improvement in respiratory function.<sup>2-9</sup> The repeated application of Abdominal FES, termed Abdominal FES training, has been hypothesised to increase abdominal muscle mass and tone, placing the diaphragm in a more efficient position for respiration.<sup>10</sup> Abdominal FES training may improve the unassisted respiratory function in patients with impaired respiration.

While there have been a limited number of studies investigating the use of Abdominal FES to improve respiratory function in patients with stroke,<sup>11</sup> traumatic brain injury<sup>12</sup> and Chronic Obstructive Pulmonary Disease (COPD),<sup>13</sup> the vast majority of clinical investigations of Abdominal FES have focused on patients with Spinal Cord Injury (SCI).<sup>10,14,15</sup> These patients commonly have paralysis or impaired function of the major respiratory muscles: namely the diaphragm, intercostal muscles and abdominal muscles. As a result, SCI is associated with reduced levels of respiratory function compared with the able bodied population, with tetraplegia resulting in an approximately 50% reduction in respiratory function.<sup>16</sup> Reduced respiratory function leaves people with an SCI unable to clear their airways through cough, often leading to respiratory complications, such as atelectasis, pneumonia and ventilatory failure,<sup>17</sup> being a primary cause of morbidity and mortality for this population.<sup>18</sup> An improvement in respiratory function has been shown to positively correlate with a reduction in respiratory complications.<sup>14</sup> If Abdominal FES is effective in improving respiratory function, then this could have a significant impact on morbidity and mortality for the SCI population.

Despite the positive results achieved in individual Abdominal FES studies in SCI, there has been no pooled analysis of the effect of Abdominal FES on respiratory function. A systematic review and meta-analysis can be used to pool results from different studies, thereby enhancing the precision of estimates of treatment effects.<sup>19</sup> The aim of this systematic review and meta-analysis was to identify whether Abdominal FES is an effective intervention to improve respiratory function in both an acute and chronic manner after SCI.

## **Methods**

### **Literature search**

Two authors (EJM, RJF) independently searched PubMed on the 23<sup>rd</sup> December 2014 for peer-reviewed articles that investigated the effect of Abdominal FES on respiratory function. The keywords used for the search were either abdominal or abdominal muscles, and electrical stimulation or functional electrical stimulation or neuromuscular electrical stimulation or muscle stimulation or stimulation, and breathing or respiratory or respiration or cough or spirometry or tidal volume or inspiratory or expiratory. Reference lists from identified articles were also hand searched for articles not returned in the initial search.

## Study selection and eligibility criteria

Articles were included if they applied Abdominal FES and measured respiratory function. Articles were excluded if they were: not in English; duplicates (or where participants in studies were not independent of a previous publication); experiments in animals; single case reports; meeting abstracts; editorials or reviews. Furthermore, to remove a significant source of heterogeneity, two studies that met the aforementioned inclusion criteria but included patients who did not have SCI were excluded from the meta-analysis.<sup>11,12</sup>

Initially, all abstracts and titles were independently reviewed (EJM, RJF) and sorted based on the predefined inclusion criteria. The full text of the studies that match this criteria were then independently reviewed (EJM, RJF) and once again sorted based on the predefined inclusion criteria. Both reviewers held a meeting to confirm the articles to be included in the review. In cases of disagreement, a third reviewer (AJM) made the final decision. Single case studies were noted and used for informational purposes, but were excluded from the analysis, so as to avoid the redundant reporting of findings. The search protocol, which was registered on the PROSPERO registry (registration number: CRD42015024218), is summarised in Figure 1.

## Measures of Respiratory Function

A number of measures of respiratory function were used to measure the efficacy of Abdominal FES in this analysis. Cough Peak Flow (CPF) is the maximum rate at which air can be exhaled from the lungs during a cough, while Peak Expiratory Flow (PEF) is the maximum rate at which air can be exhaled from the lungs when measuring from total lung capacity and exhaling as forcefully and as quickly as possible. As both CPF and PEF are measured during exhalation, they can be used to indicate the strength of the expiratory muscles. Maximum Expiratory Pressure (MEP) is the maximum pressure generated at the mouth when exhaling from total lung capacity as forcefully as possible against an occluded airway, and hence can also be used to measure the strength of the expiratory muscles. Vital Capacity ( $V_C$ ), the total volume of air exhaled after inhaling to total lung capacity and exhaling passively, and Forced Vital Capacity (FVC), the total volume of air exhaled after inhaling to total lung capacity and exhaling as forcefully as possible, can be used to evaluate the strength of the inspiratory muscles ( $V_C$  and FVC) and the expiratory muscles (FVC). These measures are closely related, with the only difference being the lower level of effort exerted during  $V_C$  exhalation.<sup>20</sup> When measuring FVC, Forced Exhaled Volume in one second ( $FEV_1$ ), which is the volume of air which can be exhaled from the lungs in the first second of a forced exhalation, can also be measured to provide an indication of the strength of the expiratory muscles. Finally, Gastric ( $P_{ga}$ ) and Esophageal Pressure ( $P_{es}$ ) can be used to measure the pleural pressures achieved during contraction of the expiratory muscles, providing another indication of the strength of the expiratory muscles.

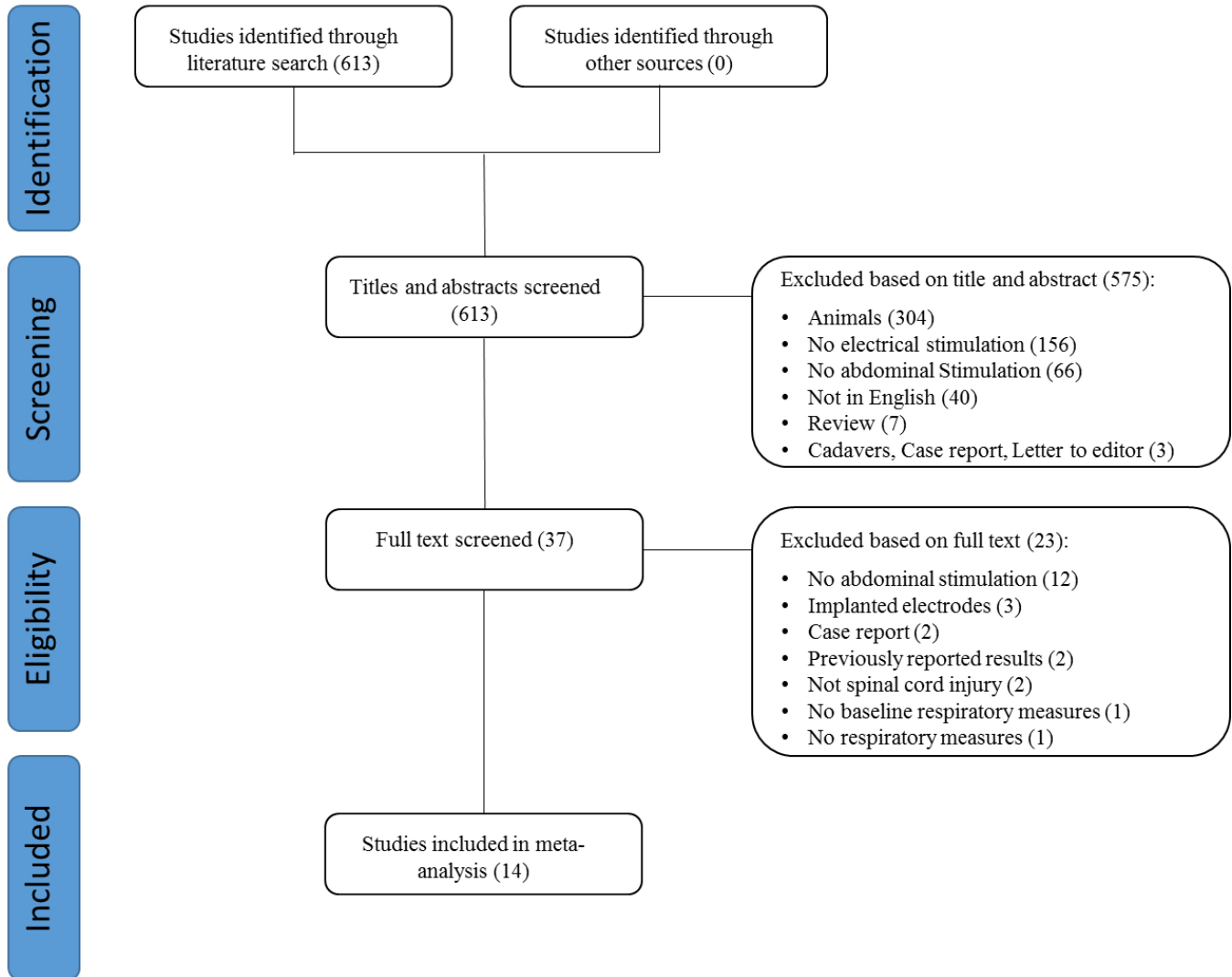


Figure 1 PRISMA flow diagram of search protocol.

## Analysis

Authors of studies that met the inclusion criteria but where a lack of information in the manuscript meant that the study could not be included in the initial meta-analysis were contacted and asked to provide additional information.<sup>2,10,15</sup> McLachlan *et al.* also provided acute data that was not published in the original manuscript.<sup>10</sup>

Studies that met inclusion criteria were classified into two broad categories, namely acute and chronic. Acute studies compared respiratory function prior to and during Abdominal FES. These studies applied a self-control study design. Chronic studies measured the chronic effect of Abdominal FES training. These studies applied either a self-control (randomised cross over) study design or a Randomised Controlled Trial (RCT) approach, with all chronic studies included in the meta-analysis applying a three phase approach. The first phase was the baseline period, during which time one or more baseline measures of respiratory function were

recorded (single time point to six weeks). The second phase was the training period, where Abdominal FES was applied over a defined time period (4-6 weeks). In the RCT a matched control group received no intervention during the training period. During the third phase, (withdrawal), respiratory function was measured immediately after the conclusion of training, with participants followed-up at time points varying between three weeks and six months.

For both acute and chronic studies, analyses were carried out using either fixed effects models, using the Inverse of the Variance (I-V) approach, or random effects models, using the DerSimonian and Laird (D-L) approach.<sup>21</sup> Model choice was determined by the between study heterogeneity of pooled results, which was quantified and assessed using the  $I^2$  statistic.<sup>22,23</sup> Where models exhibited low heterogeneity ( $I^2 < 0.3$ ), pooled models were analysed using the standard I-V weighting approach, while models exhibiting moderate to high heterogeneity ( $I^2 > 0.3$ ) were analysed using the D-L approach.<sup>21</sup>

Due to differences in baseline function between studies, estimates of effect were made using the Standardised Mean Difference (SMD) approach, applying Glass's  $\Delta$ .<sup>24</sup> This method is preferred where the intervention may potentially alter observed variability and is less susceptible to small sample bias than other SMD techniques.

Multiple models were applied to compare time points in the self-control chronic studies, with similar analyses applied to RCTs at equal time points. The reason for this stratified approach is twofold. Firstly, standard approaches to meta-analysis of self-control study designs are continuing to mature, with no standard for such a design. Furthermore, such study designs necessitate controlling or accounting for the natural recovery in respiratory function that occurs in the period immediately following an SCI.<sup>25,26</sup> Therefore, it was decided that such stratified analysis using the conservative Glass's  $\Delta$  was an acceptable methodological compromise considering the present state of the art.

A descriptive approach was used to analyse trends observed in the chronic studies, with data normalised based on minimum within study values for each measure of respiratory function. This restricted approach was employed due to the variability in baseline measures across studies and the fact that these studies did not measure respiratory function across consistent time points nor conduct the same number of tests across these time points.

Publication bias was assessed using the Begg and Mazumdar test and the Eggar approach.<sup>27,28</sup> For all statistical tests a p-value of less than 0.05 was considered significant. All statistical analyses were carried out using STATA v. 14.0 (STATA Corp, TX, USA) and associated updates.<sup>29,30</sup>

## Results

Fourteen studies that investigated the effect of Abdominal FES on respiratory function in patients with SCI were included in this review. Ten studies investigated the acute effect of

Abdominal FES,<sup>2-8,31-33</sup> while four studies investigated the chronic effect of Abdominal FES training.<sup>9,10,14,15</sup>

## **Participants**

The 14 studies included a total of 141 participants (mean age 37.8 years, 90.1% male), with 128 (mean age 37.7 years, 89.2% male) receiving Abdominal FES and 13 (mean age 38.8 years, 76.9% male) acting as controls (Table 1). None of the patients had been exposed to abdominal FES prior to participation in any of the studies. However, all patients were receiving standard SCI rehabilitation, which was likely to have included exercises aimed at strengthening the abdominal muscles.

## **Protocols**

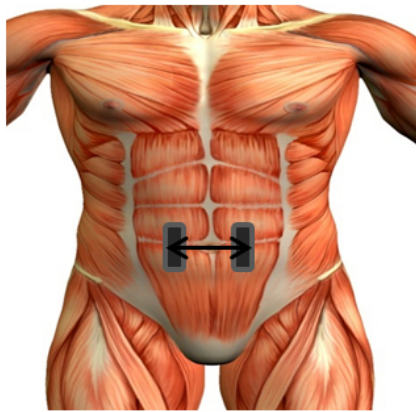
The stimulation parameters used in each study are shown in Table 1, while a graphical representation of the electrode positions used in each study is provided in Figure 2. The median maximum amplitude was 100 mA (range 100 to 450 mA), the mean pulsewidth (pulse duration) was 259  $\mu$ s (range 25 to 400  $\mu$ s) and almost all studies used a stimulation frequency of 50 Hz (Table 1). There was a lack of homogeneity in electrode position, with a range of positions used to stimulate either or both of the rectus abdominis and external oblique muscles (Figure 2).

Table 1 Characteristics of included studies. For studies that included patients with SCI, the injury level (relating to the lowest level with preserved function) and American Spinal Injuries Association Impairment Scale (AIS) grade are shown.<sup>34</sup> AIS A – No function or sensation, AIS B – No function with sensation, AIS C – Compromised function with sensation. Evaluated measures refer to measures included in the meta-analysis.

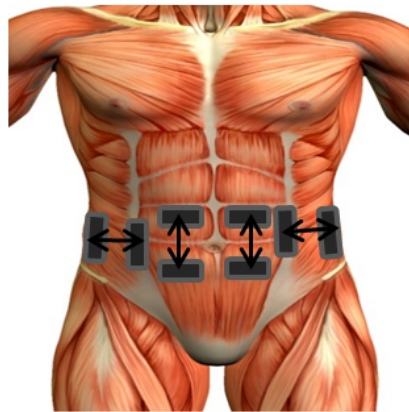
Author (Year)	Country	Design	Etiology (Injury level, AIS Grade)	Participants	Mean Age (Years)	Male (%)	Years Post Injury (Mean ± Std, min, max)	Treatment	Follow-up	Evaluated Measures	Stimulator	Stimulation parameters		
												Frequency (Hz)	Amplitude	Pulsewidth (µs)
Butler <i>et al.</i> (2011) <sup>2</sup>	Australia	Self-control	SCI (C3/4-T6, A-C)	11	45	73	9.2 ± 4.1, 0.3, 43.4	Acute	N/A	CPF, FEV <sub>1</sub> , P <sub>es</sub> , P <sub>ga</sub> , V <sub>c</sub>	DS7 (Digitimer Ltd, UK)	50	50 to 450 mA	200
Gollee <i>et al.</i> (2007) <sup>3</sup>	UK	Self-control	SCI (C4-C6, A)	4	36.8	75	1.8 ± 2.2, 0.3, 5.0	Acute	N/A	CPF	Motive 8 (Stanmore, UK)	50	30 to 100 mA	400
Jaeger <i>et al.</i> (1993) <sup>4</sup>	USA	Self-control	SCI (C4-C7, A-C)	14	34*	79*	1.7 ± 2.2, 0.1, 7.2	Acute	N/A	CPF	Custom	50	Max 110 V	300
Kandare <i>et al.</i> (2002) <sup>31</sup>	Slovenia	Case series	SCI (C0-C2, A, ventilator dependent)	3	18.3	100	< 1 year	Acute	N/A	None	Custom	45	60 to 100 mA	25
Langbein <i>et al.</i> (2001) <sup>5</sup>	USA	Self-control	SCI (C5-T7, A-D)	10	50.4	100	12.3 ± 8.7, 1, 27	Acute	N/A	FEV <sub>1</sub> , FVC, PEF	EMPI Focus (EMPI Inc., USA)	50	1 to 100 mA	250
Lin <i>et al.</i> (1998) <sup>32</sup>	Taiwan	Self-control	SCI (C4-T12, A-B)	24	36.1	N. G.	9.6 ± 1.6	Acute	N/A	CPF	Respond II (EMPI Inc., USA)	50	N. G.	300
Linder (1993) <sup>6</sup>	USA	Self-control	SCI (C4-C7, A-B)	8	38	100	12.3 ± 9.3	Acute	N/A	MEP	N. G.	50	N. G.	300
Sorli <i>et al.</i> (1996) <sup>7</sup>	Slovenia	Self-control	SCI (C6/7, A)	1	22	0	0.75	Acute	N/A	None	Custom	50	20 to 100 mA	350
Spivak <i>et al.</i> (2007) <sup>33</sup>	Israel	Self-control	SCI (C4-C7, A-C)	10	40	100	4.7 ± 9.9, 0.1, 32	Acute	N/A	FVC, PEF	Quick Off ('B' & 'B' Medical Technologies Inc., USA)	50	100 mA	300
Stanic <i>et al.</i> (2000) <sup>8</sup>	Slovenia	Self-control	SCI (C4-C6/7, B-D)	5	N.G.	100	N.G.	Acute	N/A	None	Custom	50	N. G.	350
Cheng <i>et al.</i> (2006) <sup>14</sup>	Taiwan	RCT	SCI (C4-C7, A-B)	26 (13 Abdominal FES)	36.8	91	0.2 ± 0.1	30 mins/d, 5 d/wk, 4 wks	6 mo	FEV <sub>1</sub> , FVC, MEP, PEF, V <sub>c</sub>	Respond Select (EMPI Inc., USA)	50	1 to 100 mA	300
McBain <i>et al.</i> (2013) <sup>15</sup>	Australia	Randomised cross over	SCI (C4-T5, A-C)	15	45	100	11.9 ± 4.3, 0.3, 41.1	50 coughs/d, 5d/wk, 6 wks	6 wk	FEV <sub>1</sub> , FVC, PEF, P <sub>es</sub> , P <sub>ga</sub> , V <sub>c</sub>	DS7 (Digitimer Ltd, UK)	50	N. G.	200
McLachlan <i>et al.</i> (2013) <sup>10</sup>	UK	Self-control	SCI (C3-C6, A-C)	12	38.6	92	1.4 ± 2.2, 0.2, 7.8	20-60 min/d, 4 d/wk, 4 wks	3 wk	FVC, FEV <sub>1</sub> , MEP, PEF	Rehastim (Hasomed, Germany)	30	30 to 100 mA	50
Zupan <i>et al.</i> (1997) <sup>9</sup>	Slovenia	Randomised cross over	SCI (C4-C7, A-C)	13	26.9	85	1.3, 0.3, 10	20-30 mins, 2 times/d, 6 d/wk, 4 wks	No	None	N. G.	50	Max 110V	300

\* Results are mean of 24 participants initially recruited for the study. N.G.- Not given. Std- Standard Deviation.

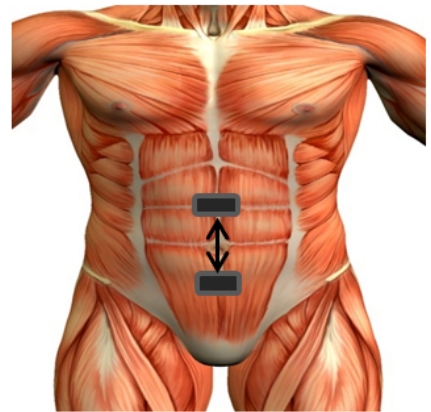




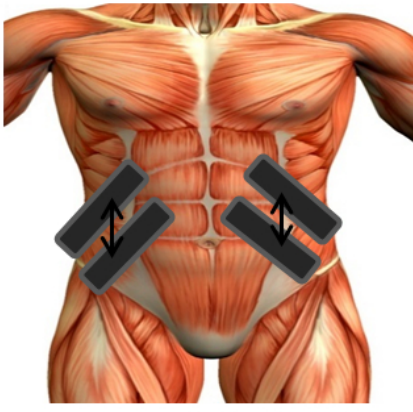
(a) Jaeger et al.<sup>4</sup>



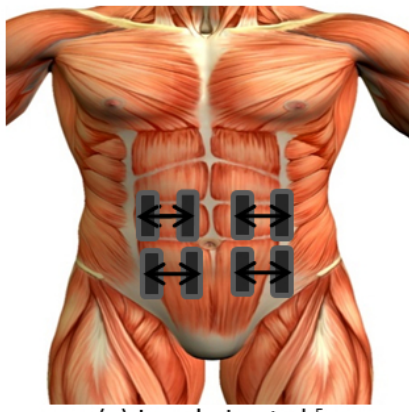
(b) Kandare et al.<sup>31</sup>



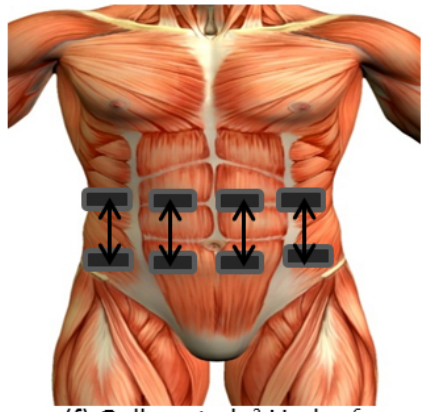
(c) Sorli et al.<sup>7</sup>



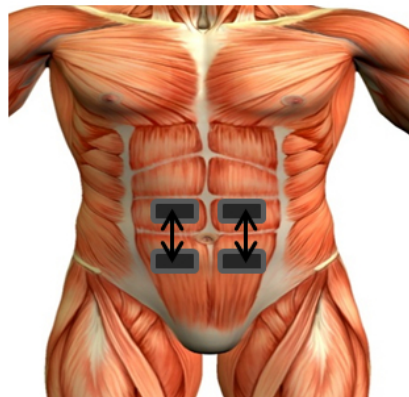
(d) Butler et al.,<sup>2</sup> McBain et al.<sup>15</sup>



(e) Langbein et al.<sup>5</sup>



(f) Gollee et al.,<sup>3</sup> Linder,<sup>6</sup>  
McLachlan et al.<sup>10</sup>



(g) Cheng et al.,<sup>14</sup> Lin et al.,<sup>32</sup> Spivak et al.,<sup>33</sup> Stanic et al.,<sup>8</sup> Zupan et al.<sup>9</sup>

Figure 2 Electrode positions used to deliver Abdominal FES

## Respiratory Measures

### Acute effect

#### Cough and Respiratory Muscle Strength

The application of Abdominal FES was found to lead to a significant increase in CPF (Figure 3A).<sup>2-4,15</sup> Despite Butler *et al.*<sup>2</sup> and McBain *et al.*<sup>15</sup> both finding that the application of Abdominal FES led to a statistically significant increase in  $P_{ga}$  and  $P_{es}$ , significant heterogeneity ( $I^2=96.5\%$ ,  $p=0.000$ ) between both studies resulted in low confidence in the pooled estimate (Figure 3B). Two studies investigated the acute effect of Abdominal FES on MEP.<sup>6,10</sup> While Linder *et al.*<sup>6</sup> found a significant increase in MEP with Abdominal FES, there was low confidence in the pooled estimate (Figure 3C).

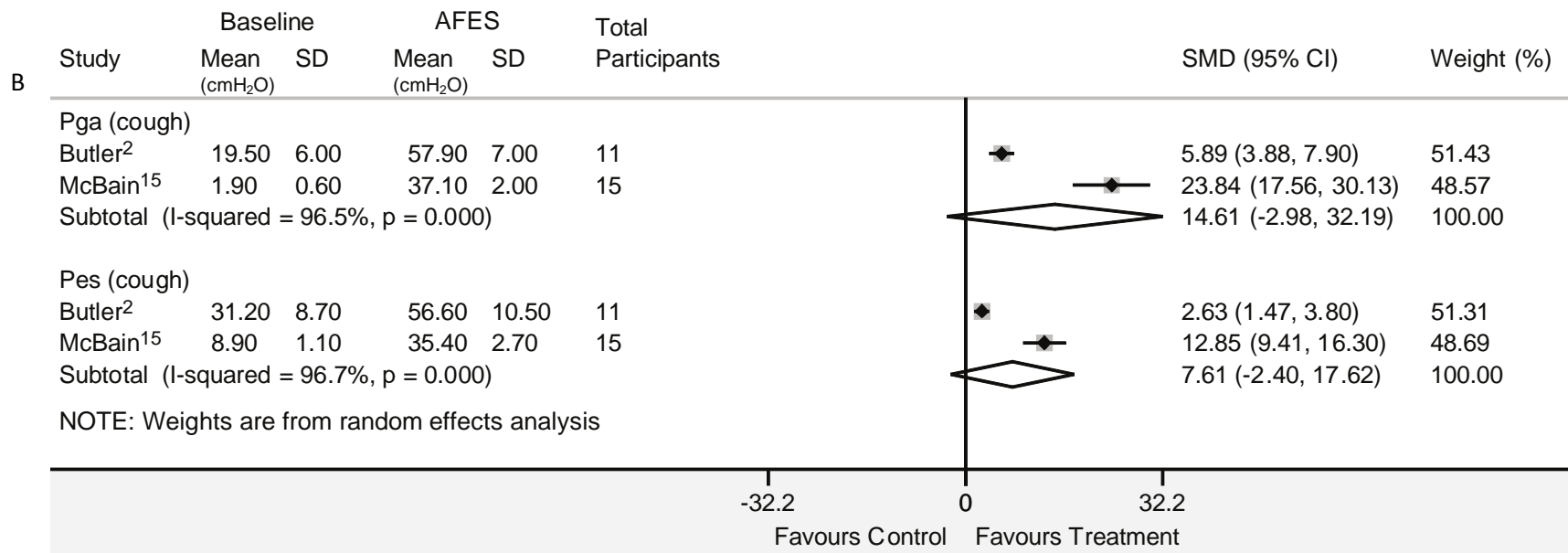
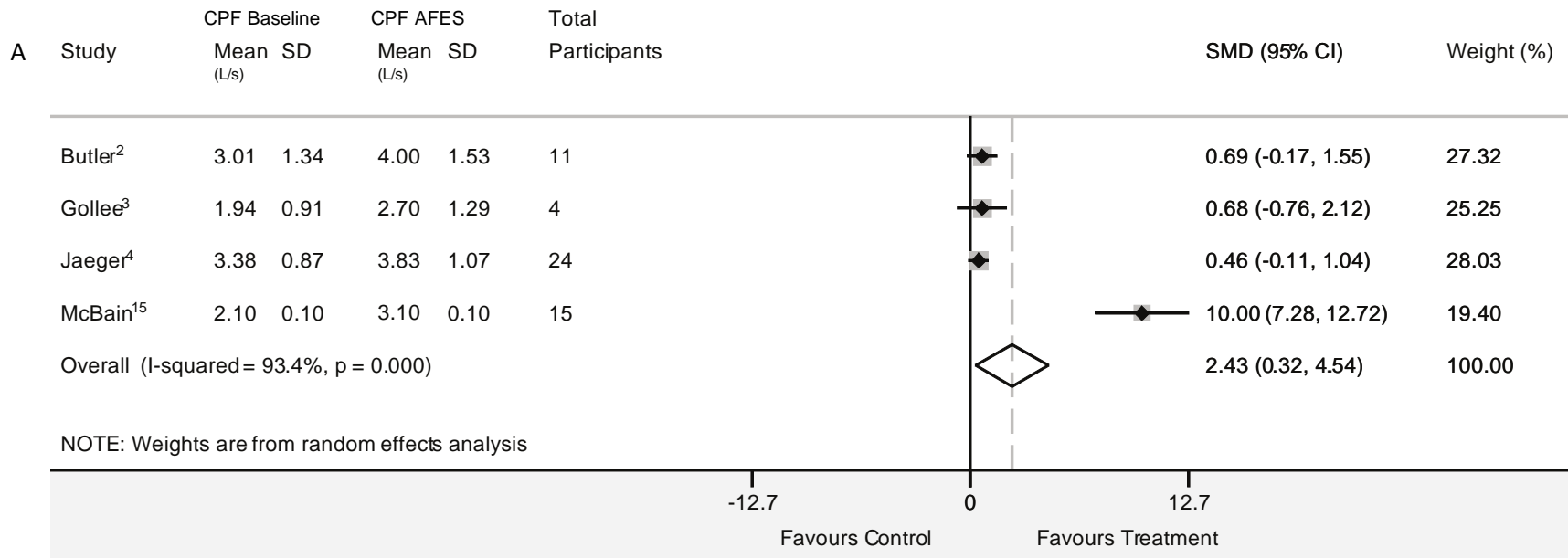
#### Spirometry

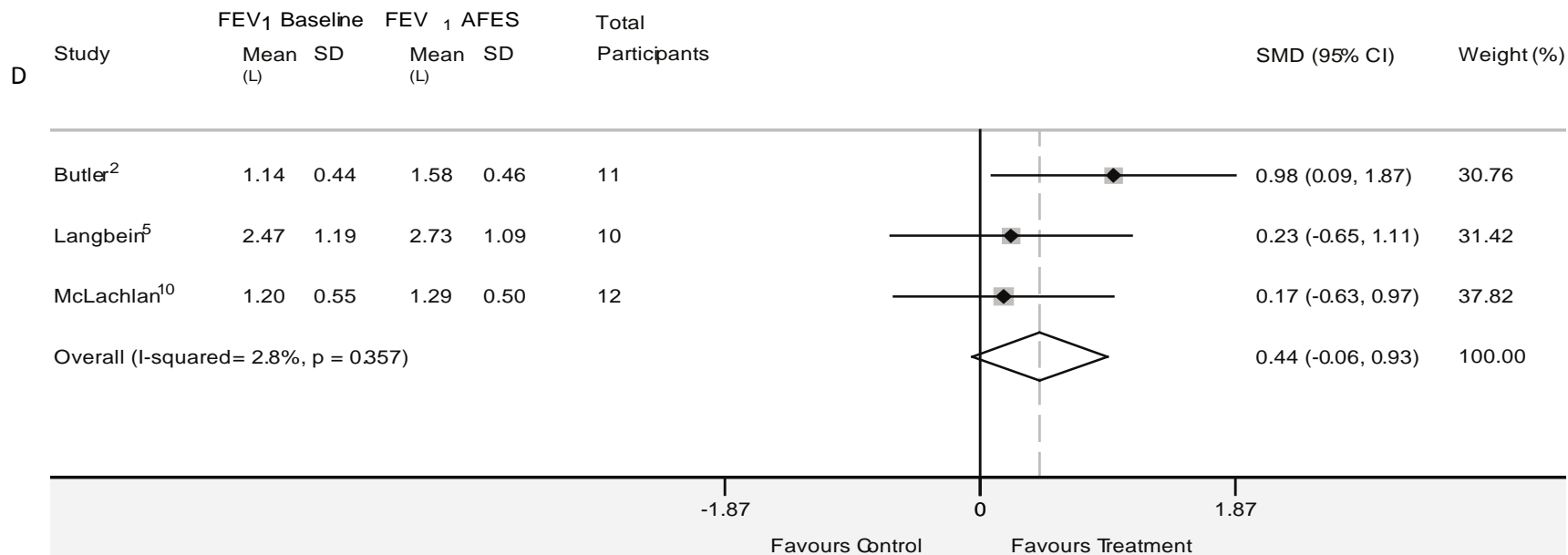
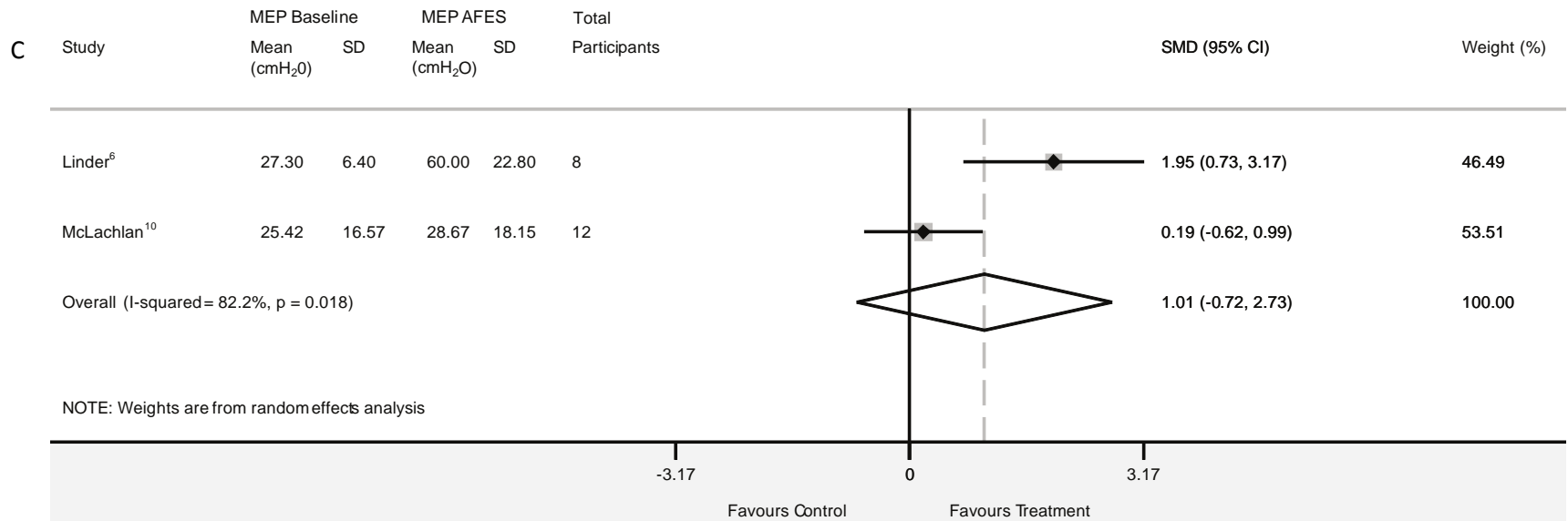
Three studies investigated the acute effect of Abdominal FES on  $FEV_1$ .<sup>2,5,10</sup> While Butler *et al.*<sup>2</sup> were the only study to find a significant effect of Abdominal FES on  $FEV_1$ , the pooled effect approached significance (Figure 3D). While the three studies that investigated the acute effect of Abdominal FES on FVC and PEF displayed homogeneity ( $I^2=0.0\%$ ,  $p=0.585$  and  $I^2=0.0\%$ ,  $p=0.870$ , respectively), there was no treatment effect (Figure 3E and 3F).<sup>5,10,33</sup>

### Chronic effect

#### Forced Vital Capacity

A significant increase in FVC was observed after Abdominal FES training was applied in three studies ( $p=0.043$ ),<sup>10,14,15</sup> while Cheng *et al.*<sup>14</sup> demonstrated no longitudinal change for a control group who underwent no training ( $p=0.899$ ) (Table 2). All three studies also observed a continued improvement after training (Figure 4A). Cheng *et al.*<sup>14</sup> also found a significant difference between the intervention and control group immediately post training ( $p=0.020$ ) and a trend towards significance six months after training ( $p=0.128$ ). Cheng *et al.*<sup>14</sup> and McBain *et al.*<sup>15</sup> observed a significant increase in  $V_c$  after Abdominal FES training ( $p=0.013$ ), while Cheng *et al.* demonstrated no longitudinal change for a control group ( $p=0.760$ ) (Table 2). After the intervention was removed Cheng *et al.* observed an increase in  $V_c$  for both the control and intervention at three and six months post training, however McBain *et al.* observed a decrease in  $V_c$  six weeks post training (Figure 4B). Cheng *et al.* also found that the difference between the intervention and control group immediately post and six months after training approached significance ( $p=0.128$  and  $p=0.101$ , respectively) (Table 3).





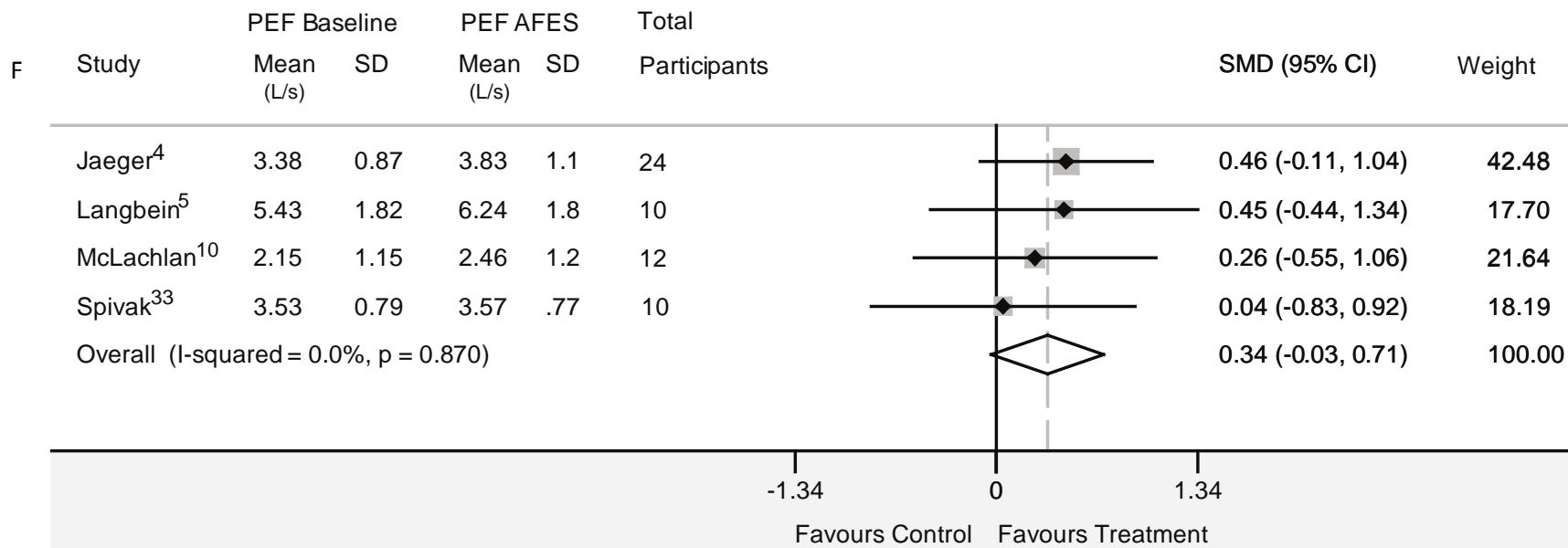
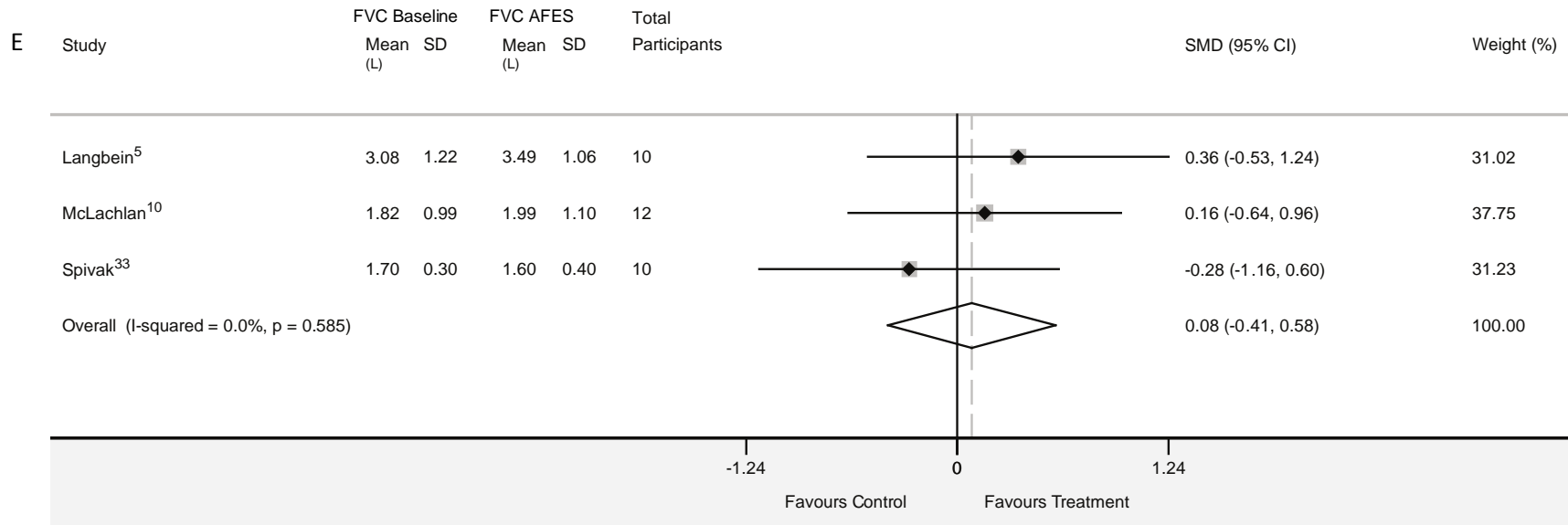


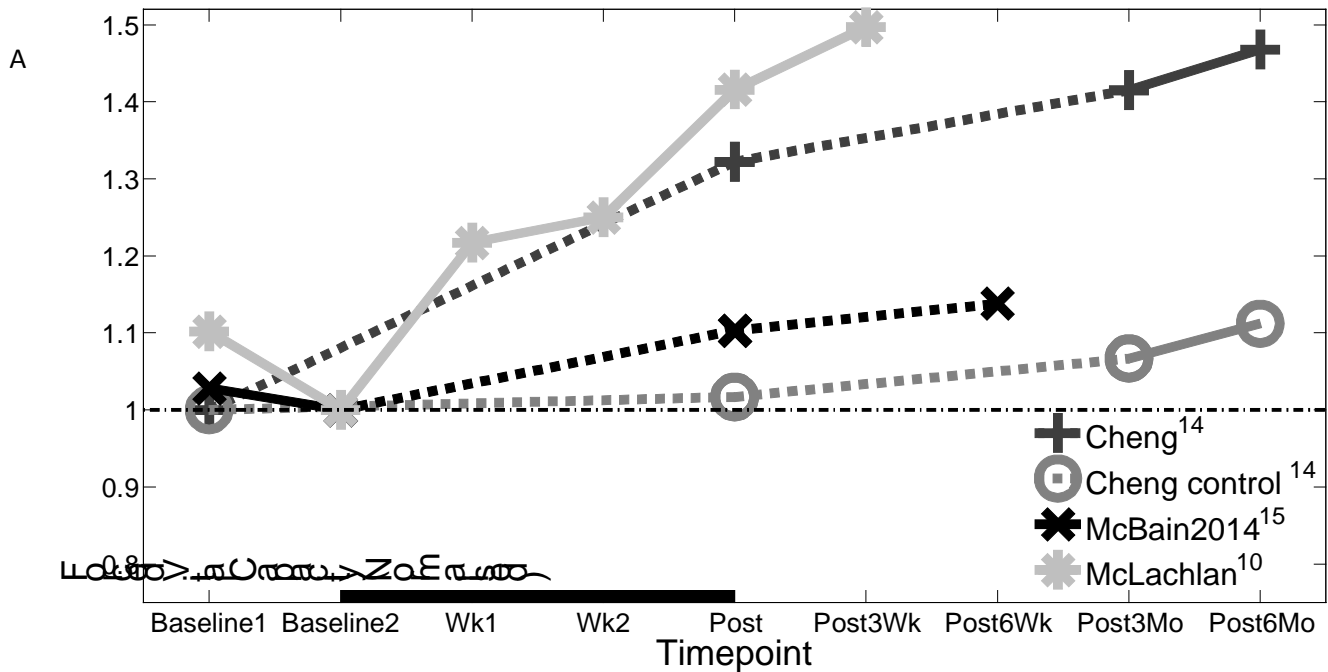
Figure 3 Acute effect of Abdominal FES (AFES) on respiratory function. A- Cough Peak Flow (CPF), B- Gastric ( $P_{ga}$ ) and Esophageal Pressure ( $P_{es}$ ) during cough, C- Maximum Expiratory Pressure (MEP), D- Forced Exhaled Volume in One Second ( $FEV_1$ ), E- Forced Vital Capacity (FVC), F- Peak Expiratory Flow (PEF). Standardised Mean Difference (SMD) is shown on x-axis. A Positive SMD indicates that the treatment effect favours the intervention, while a negative SMD indicates that the treatment effect favours the control (no intervention). For Figures A, B and C pooled analysis uses a random effects model, while for Figures D, E and F pooled analysis uses a fixed effects model. Note: data for McLachlan *et al.*<sup>10</sup> was provided by the authors and data for McBain *et al.*<sup>15</sup> only published results to one significant figure.

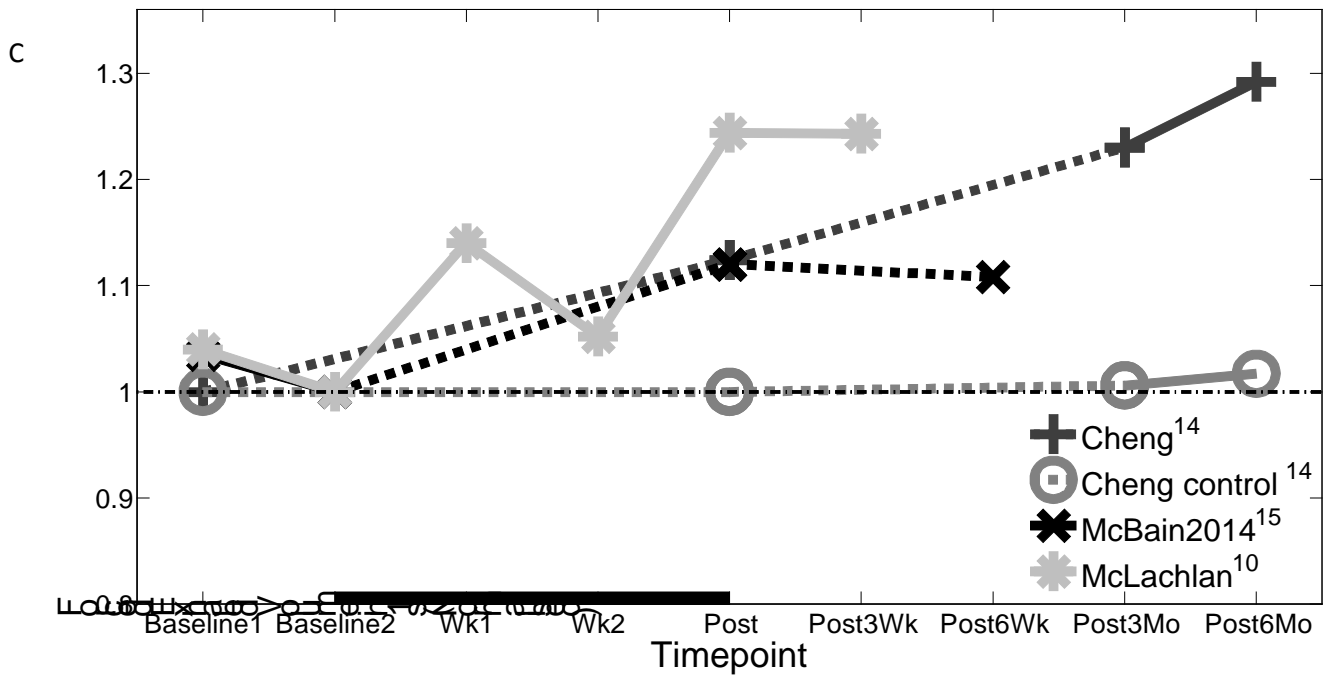
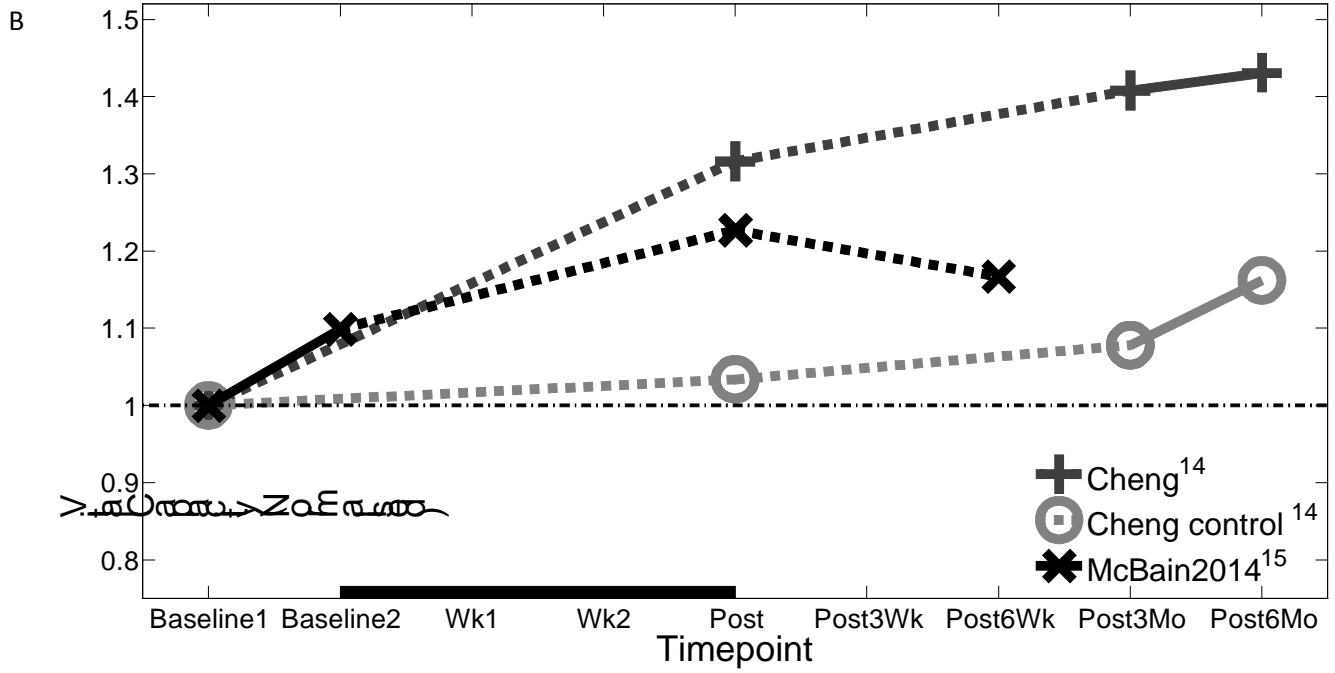
Table 2 Longitudinal effect of Abdominal FES training on respiratory function between baseline and conclusion of treatment. Pooled analysis of FVC, VC, FEV1 and PEF uses a fixed effects model, while pooled analysis of MEP uses a random effects model. A positive Standardised Mean Difference (SMD) favours the intervention, while a negative SMD favours the control. FVC- Forced Vital Capacity,  $V_c$ - Vital Capacity,  $FEV_1$ - Forced Exhaled Volume in one second, PEF- Peak Expiratory Flow and MEP- Maximum Expiratory Pressure.

Measure	Author	Modality	Participants	SMD	CI	Weight	p-value
FVC (L)	Cheng <sup>10</sup>	Stim	13	0.786	-0.045 to 1.616	29.93	
	McBain <sup>12</sup>	Stim	15	0.213	-0.507 to 0.933	39.82	
	McLachlan <sup>11</sup>	Stim	12	0.491	-0.335 to 1.317	30.26	
I-V pooled SMD ( $I^2 = 0.00$ , $df = 2$ , $p = 0.593$ )				0.469	0.014 to 0.923		0.043
	Cheng <sup>10</sup>	Control	13	0.05	-0.719 to 0.819		0.899
$V_c$ (L)	Cheng <sup>10</sup>	Stim	13	0.786	-0.045 to 1.616	45.19	
	McBain <sup>12</sup>	Stim	15	0.642	-0.112 to 1.396	54.81	
I-V pooled SMD ( $I^2 = 0.00$ , $df = 1$ , $p = 0.802$ )							0.013
	Cheng <sup>10</sup>	Control	13	0.12	-0.650 to 0.890		0.760
$FEV_1$ (L)	Cheng <sup>10</sup>	Stim	13	0.314	-0.465 to 1.093	32.46	
	McBain <sup>12</sup>	Stim	15	0.258	-0.464 to 0.981	37.78	
	McLachlan <sup>11</sup>	Stim	12	0.35	-0.463 to 1.163	29.77	
I-V pooled SMD ( $I^2 = 0.00$ , $df = 1$ , $p = 0.986$ )				0.304	-0.140 to 0.748		0.180
	Cheng <sup>10</sup>	Control	13	0	-0.769 to 0.769		1.000
PEF (L/s)	Cheng <sup>10</sup>	Stim	13	1.078	0.196 to 1.959	27.41	
	McBain <sup>12</sup>	Cough	15	0.431	-0.302 to 1.165	39.61	
	McLachlan <sup>11</sup>	Stim	12	0.18	-0.624 to 0.983	32.98	
I-V pooled SMD ( $I^2 = 12.4$ , $df = 2$ , $p = 0.319$ )				0.526	-0.064 to 1.987		0.026
	Cheng <sup>10</sup>	Control	13	-0.014	-0.783 to 0.754		0.971
MEP (cmH <sub>2</sub> O)	Cheng <sup>10</sup>	Stim	13	0.968	0.107 to 1.828	46.36	
	McLachlan <sup>11</sup>	Stim	12	0	-0.800 to 0.800	53.64	
D-L pooled SMD ( $I^2 = 61.6$ , $df = 1$ , $p = 0.107$ )				0.47	-0.478 to 1.418		0.134
	Cheng <sup>10</sup>	Control	13	0.262	-0.514 to 1.038		0.508

Table 3 Comparison of respiratory function immediately and six months post Abdominal FES training between intervention and control groups. A positive Standardised Mean Difference (SMD) favours the intervention, while a negative SMD favours the control. FVC- Forced Vital Capacity, V<sub>c</sub>- Vital Capacity, FEV<sub>1</sub>- Forced Exhaled Volume in one second, PEF- Peak Expiratory Flow and MEP- Maximum Expiratory Pressure.

Measure	Author	Modality	Participants	Time point	SMD	CI	p-value
FVC (L)	Cheng <sup>10</sup>	Stim	13	Immediately post training	0.629	-0.180 to 1.437	0.128
				6 months post training	1.04	0.166 to 1.914	0.020
V <sub>c</sub> (L)	Cheng <sup>10</sup>	Stim	13	Immediately post training	0.629	-0.180 to 1.437	0.128
				6 months post training	0.683	-0.133 to 1.499	0.101
FEV <sub>1</sub> (L)	Cheng <sup>10</sup>	Stim	13	Immediately post training	0.371	-0.412 to 1.154	0.353
				6 months post training	0.052	-0.717 to 0.822	0.894
PEF (L/s)	Cheng <sup>10</sup>	Stim	13	Immediately post training	1.144	0.250 to 2.039	0.012
				6 months post training	1.337	0.401 to 2.274	0.005
MEP (cmH <sub>2</sub> O)	Cheng <sup>10</sup>	Stim	13	Immediately post training	0.72	-0.101 to 1.541	0.085
				6 months post training	1.026	0.155 to 1.898	0.021







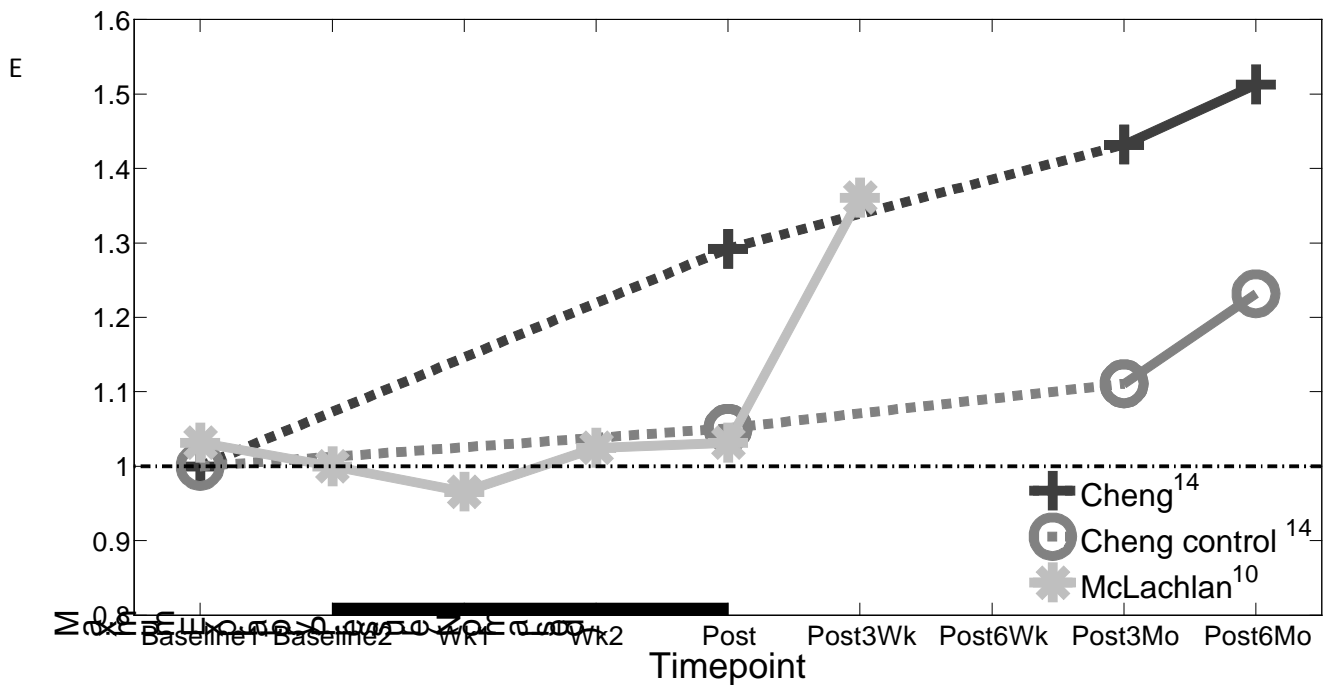
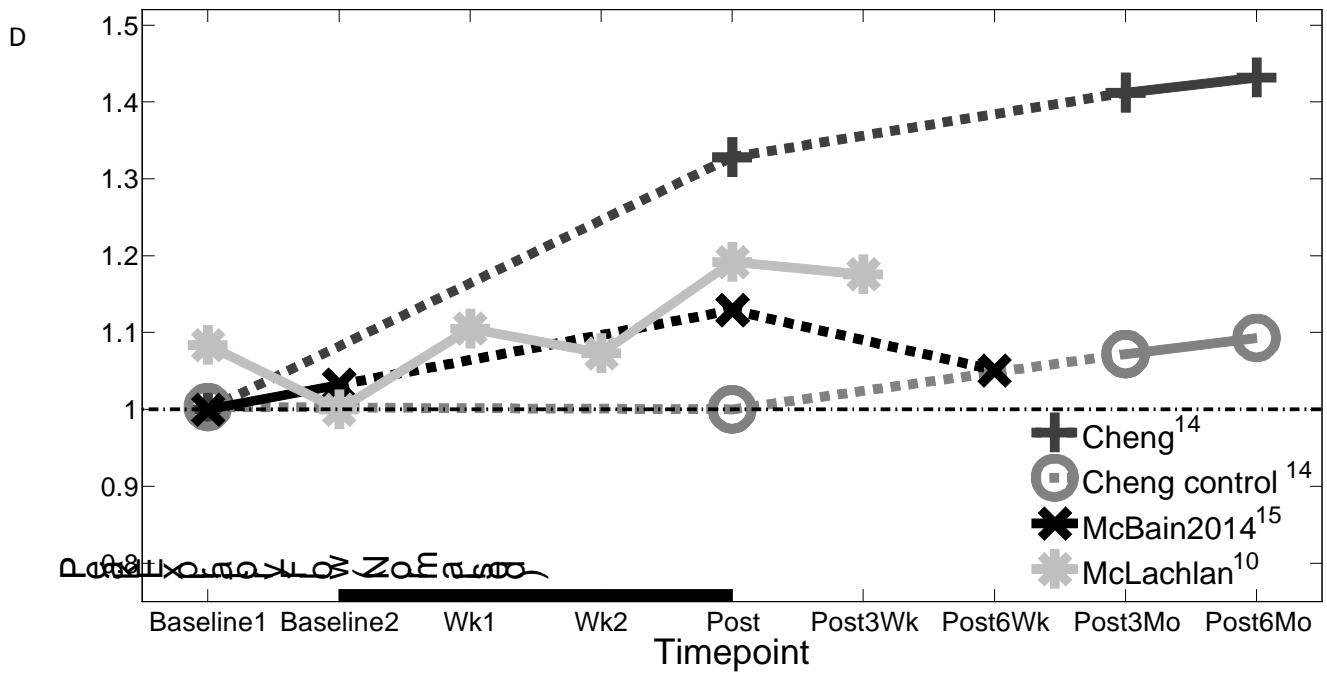


Figure 4 Effect of Abdominal FES training on unassisted respiratory function. A- Forced Vital Capacity, B- Vital Capacity, C- Forced Exhaled Volume in 1 second, D- Peak Expiratory Flow, E- Maximum Expiratory Pressure. Data is normalised based on minimum within study values for each measure of respiratory function. Black bar along bottom of plot represents period of

Abdominal FES training. Solid lines between time points indicate consecutive measurements, dotted lines indicate measurements that span more than 1 time point. Note: Time between Baseline 1 and Baseline 2 and Baseline 2 and Post are not equal for each study.

### **Forced Exhaled Volume in One Second**

When analysing the three studies that investigated the effect of Abdominal FES training on FEV<sub>1</sub>, the pooled effect was not found to be significant ( $p=0.180$ ) (Table 2). Cheng *et al.* found a continued increase in FEV<sub>1</sub> after training, while McLachlan and McBain found a decrease in this measure after training (Figure 4C). Cheng *et al.* also found no difference between the intervention and control group immediately post or six months after training ( $p=0.353$  and  $p=0.894$ , respectively) (Table 3).

### **Peak Expiratory Flow**

The pooled treatment effect of three studies that investigated the effect of Abdominal FES training on PEF suggested a significant treatment effect ( $p=0.026$ ), while Cheng *et al.* demonstrated no longitudinal change for a control group who underwent no training ( $p=0.971$ ) (Table 2). Cheng *et al.* report further increases in PEF after Abdominal FES training, while McLachlan *et al.* and McBain *et al.* report a decrease in PEF at the first time point after training (Figure 4D). Cheng *et al.* also found a significant difference between the PEF of the intervention and control group immediately after and six months after training ( $p=0.012$  and  $p=0.005$ , respectively) (Table 3).

### **Maximum Expiratory Pressure**

McLachlan *et al.* and Cheng *et al.* investigated the effect of Abdominal FES training on MEP, with the pooled effect not found to be significant ( $p=0.134$ ) (Table 2). McLachlan *et al.* observed large variability in MEP, with little change over the training period followed by a large increase during the three week post training period, while Cheng *et al.* observed a substantial increase in MEP between 3 months and 6 months post training (Figure 4E). Cheng *et al.* did observe a statistically significant difference between the MEP of intervention and control participants six months after training ( $p=0.021$ ) and a trend towards significance immediately after training ( $p=0.085$ ) (Table 3).

### **Publication Bias**

Analysis of publication bias identified a statistically significant result in acute PEF (Begg and Mazumdar  $z = -2.04$ ,  $p = 0.042$ ). All other measures were either not statistically significant or could not be calculated due to the small number of publications associated with particular endpoints. We reason that the PEF result is not indicative of publication bias, per se, but rather a reflection of small sample size in the included studies.

## **Discussion**

## Acute effect

The included literature suggests that Abdominal FES can be used to achieve an acute improvement in CPF after SCI, while the acute effect of Abdominal FES on FEV<sub>1</sub> approached significance. Furthermore, it would appear that electrode position did not affect these changes, with Butler et al.<sup>2</sup> and Gollee et al.<sup>3</sup> finding similar increases in CPF (SMD 0.69 versus 0.68), despite Butler et al. using only four electrodes compared to Gollee et al.'s eight. McLachlan et al.<sup>10</sup> and Langbein et al.<sup>5</sup> found similar increases in FEV<sub>1</sub> (SMD 0.17 versus 0.23), despite McLachlan et al. using eight electrodes to stimulate both the rectus abdominis muscles and the external oblique muscles while Langbein et al. used eight electrodes to stimulate only the rectus abdominis muscles (Figure 2). However, low participant numbers and a lack of homogeneity across the included studies means that these results must be interpreted with caution, with the low participant numbers meaning that individual studies have the potential to skew results. This problem is highlighted when interpreting the acute effect of Abdominal FES on CPF, where despite three of the four included studies not finding a significant increase in this measure, the large increase in CPF found by McBain *et al.*<sup>15</sup> may be the sole reason for finding significance (Figure 3A). When investigating potential reasons for this difference it was found that McBain et al.<sup>15</sup> used the same electrode placement as Butler et al.<sup>2</sup> (Figure 2) in addition to very similar patients and stimulation parameters (Table 1) and measurement techniques, yet the results were markedly different (SMD 10.00 versus 0.69). This suggests that there were unidentified methodological differences that could have resulted in the variability between the studies. Due to the heterogeneity of SCI, it is possible that the study populations may vary between studies that are applying the same inclusion and exclusion criteria.

## Chronic effect

When examining the chronic effect of Abdominal FES training, the included literature suggests that Abdominal FES training leads to an improvement in FVC, V<sub>C</sub> and PEF after SCI. However, the long-term effect of Abdominal FES training remains to be established. While a continued improvement in FVC and MEP after the cessation of training was observed in all studies that investigated these measures, the improvements in V<sub>C</sub>, FEV<sub>1</sub> and PEF observed by Cheng *et al.*<sup>14</sup> after cessation of training appear to contradict the decreases in these measures observed by McLachlan *et al.*<sup>10</sup> and McBain *et al.*<sup>15</sup> Therefore, further work is needed to establish the long-term effect of Abdominal FES training and whether any of the chronic improvements reported here are maintained past the end points of the included studies.

The aim of abdominal FES training is to reduce the likelihood of respiratory complications by preventing the build-up of secretions in the airways. In two separate publications, Bach et al. state that the minimum CPF needed to clear secretions is 2.67 L/s<sup>35</sup> and that patients with a CPF of greater than 4.5 L/s are at less risk of developing acute respiratory failure.<sup>36</sup> However, Cheng et al.<sup>14</sup> were the only authors to directly investigate the use of abdominal FES to reduce respiratory complications, demonstrating a statistically significant decrease in respiratory

complications in an intervention group who received four weeks of Abdominal FES training. During the intervention period the FVC, FEV<sub>1</sub> and PEF of this intervention group increased by 0.55 L, 0.22 L and 0.97 L/s, respectively. Due to the reduction in respiratory complications associated with these improvements in respiratory function, these levels of improvement can be regarded as clinically significant and may be a beneficial benchmark for future abdominal FES studies.

## Physiology of Abdominal FES

CPF and FEV<sub>1</sub> are forced expiratory manoeuvres and are both dependent on the intrathoracic pressure generated during exhalation. The acute effect of Abdominal FES on CPF and FEV<sub>1</sub> found in this review can therefore most likely be explained by the fact that Abdominal FES has been shown to increase intrathoracic pressure in patients with SCI.<sup>2,37</sup>

The physiology of the chronic effect of Abdominal FES is less well understood. Maximising FVC and PEF relies on generating the greatest MEP, which is dependent on expiratory muscle strength. As the thickness and hence strength of the abdominal muscles has been shown to be reduced in SCI,<sup>38</sup> one explanation for the chronic increases in FVC and PEF reported here is that even for patients with complete paralysis of the abdominal muscles, Abdominal FES training thickens and strengthens the abdominal muscles, altering the passive biomedical properties of the respiratory system.<sup>10</sup> Such strengthening of muscles after FES training has been demonstrated through a shift in the force frequency curve,<sup>39</sup> increased muscle blood supply<sup>40</sup> and muscle fibre type conversion towards more fatigue resistant fibres.<sup>40,41</sup> McLachlan et al.<sup>10</sup> propose that this strengthening of the abdominal muscles leads to greater support of the abdominal contents, which act as a fulcrum as the diaphragm contracts, placing the diaphragm in a more efficient mechanical position to expand the lower lung after Abdominal FES training. There is also evidence in the literature to suggest that exercise contributes to an increase in brain-derived neurotrophic factor, which may promote synaptic and functional plasticity within the brain and spinal cord.<sup>42,43</sup> While currently postulation, such corticospinal plasticity may be the reason for the continued increase in respiratory function observed after the cessation of abdominal FES.

## Current Limitations

While the main focus of the included studies was to improve respiratory function, the driver for such an improvement is improved sputum clearance and an associated reduction in respiratory complications. Cheng *et al.*<sup>14</sup> were the only authors to investigate the impact of Abdominal FES on rates of respiratory complications. As respiratory complication rates are ultimately the primary clinical outcome measure to assess the efficacy of Abdominal FES, future Abdominal FES studies, particularly those that apply an Abdominal FES training program, should strive to investigate this effect.

Along with low participant numbers, a lack of standardised protocol was a significant burden to fully establishing the acute and chronic treatment effect of Abdominal FES. For both study

types, the range of stimulation devices, stimulation parameters and electrode positions used in the included studies is likely to have contributed to some of the variability observed in the meta-analysis. However, it is worth noting that McBain *et al.*<sup>44</sup> have demonstrated that CPF plateaued when increasing stimulation intensity, suggesting that stimulation intensity alone may not be the only factor causing this variation. Only three of the included studies<sup>9,14,15</sup> employed a random allocation of participants and only one study<sup>14</sup> used control groups. Additionally, this was the only study that blinded the assessor and no studies blinded the participants to the intervention. This lack of blinding and randomisation may create a bias in the results, again making it difficult to fully ascertain the acute or chronic effect of Abdominal FES.

## **Future Research**

To enable easier comparisons of studies, future Abdominal FES studies should strive to use standardised protocols, particularly with regards to electrode placement, stimulation parameters, inclusion and exclusion criteria and training period. Standardisation of these factors should remove a significant amount of the variability seen in the studies reported to date. Various solutions exist to facilitate such standardisation. Firstly, McCaughey *et al.*<sup>45</sup> propose the use of electrical stimulation to detect the motor points of the abdominal muscles, enabling standardisation of electrode placement. A number of techniques have also been proposed to standardise the muscle contraction achieved with abdominal FES. Butler *et al.*<sup>2</sup> and McBain *et al.*<sup>15</sup> increased stimulation intensity until a  $P_{ga}$  of 40 cmH<sub>2</sub>O was achieved. While this technique allows quantitative standardisation, it requires use of an intrusive nasal catheter. Most studies included in this review adjusted stimulation parameters until a strong, even, visible contraction of the abdominal muscles was achieved. While this may be less precise than the method used by Butler *et al.* and McBain *et al.*, it should enable a consistent muscle contraction to be achieved in a non-intrusive fashion. This review also identifies that abdominal FES can be used to improve the respiratory function of a wide range of SCI patients, ranging from ventilator dependent tetraplegic patients,<sup>31</sup> to non-ventilator dependent paraplegic patients,<sup>2,15</sup> with no obvious exclusion criteria identified from either a safety or efficacy perspective. However, further studies are required to identify the patient groups that would benefit most from abdominal FES. Finally, the majority of abdominal FES training protocols have applied stimulation for four weeks, with varied follow-up times.<sup>9,10,14</sup> While all studies observed an improvement in respiratory function over this period, further study is required to ascertain the optimum abdominal FES training duration and to establish a standard follow-up time post intervention.

Standardisation of the reporting of results is also required. A number of the included studies reported incomplete results, particularly pertaining to a lack of standard deviations and confidence intervals, which meant that they could not be included in the analysis. Studies also employed a range of statistical analysis techniques, with different levels of statistical power. The correct use of standardised statistics would enable the greatest possibility of finding a

treatment effect. While not a panacea, a potential solution to the problem of the low participant numbers and lack of standard protocol observed in the included studies is multi-centre RCTs, which use common protocols.

While not included in the meta-analysis due to a lack of data, three studies have reported that Abdominal FES led to a significant acute increase in Tidal Volume ( $V_T$ ) for participants with an SCI,<sup>3,7,8</sup> indicating that this measure may be worthy of further exploration. Kandare *et al.*<sup>31</sup> also demonstrated that Abdominal FES could be used to support respiration for patients who lacked spontaneous ventilation, with the intervention able to provide an adequate  $V_T$  for up to three and a half minutes. This indicates that Abdominal FES may be a useful short term alternative or back up to mechanical ventilation. While outside the scope of this review, two articles have also reported that Abdominal FES can be used to assist ventilator weaning for patients with SCI.<sup>46,47</sup> Further research may indicate that this intervention is suitable for other ventilator dependent patient groups. Finally, Butler *et al.*<sup>2</sup> and Lin *et al.*<sup>32</sup> showed that combining Abdominal FES with an abdominal binder led to an acute increase in CPF, with Lin *et al.* finding that for 12 tetraplegic patients this increase was significantly greater than that achieved using the binder alone. A further meta-analysis is required to compare the increases in respiratory function achieved using either an abdominal binder or Abdominal FES.

As Abdominal FES can be used to activate paralysed muscles, the majority of Abdominal FES studies have focused on patients with SCI. While the results with this patient group are promising, there are likely to be other patient groups who would benefit from Abdominal FES. Ito *et al.*<sup>13</sup> reported that Abdominal FES could be used to achieve an acute improvement in Tidal Volume  $V_T$  for patients with Chronic Obstructive Pulmonary Disease (COPD). Jung *et al.* demonstrated that the use of Abdominal FES training with patients with stroke could be used to achieve a significant increase in FEV<sub>1</sub> and PEF compared to matched controls.<sup>11</sup> Finally, Na *et al.* demonstrated that Abdominal FES training could be used to achieve a statistically significant increase in FVC, FEV<sub>1</sub> and CPF of patients with traumatic brain lesion, while no increase in these measures was seen in a matched control group who received no intervention.<sup>12</sup> This indicates a potential new pathway for Abdominal FES research, which may be applicable for a larger range of patient groups.

## **Conclusion**

The included literature indicates that Abdominal FES can improve respiratory function in an acute and long term manner after SCI, with Abdominal FES found to cause an acute improvement in CPF and Abdominal FES training found to lead to a chronic increase in unassisted  $V_C$ , FVC and PEF. However, a lack of homogeneity across the studies and low participant numbers made it difficult to fully establish the treatment effect. Therefore, further randomised control trials that follow a standardised protocol and recruit larger numbers of participants are required to fully quantify the efficacy of Abdominal FES.

## **Conflict of Interest**

AJM is employed by Liberate Medical LLC, a medical device company that is developing an abdominal muscle stimulator. EJM and RF received financial support from Liberate Medical LLC to conduct this review. This work was supported by the Engineering and Physical Sciences Research Council (EJM, grant:EP/P50418X/1).

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