

1 **Vascular adaptations in non-stimulated areas during hybrid cycling**
2 **or handcycling in people with a spinal cord injury:**
3 **a pilot study of 10 cases**

4 **Vascular adaptations during hybrid- or handcycling**

5 **Key words:** *Spinal cord injury, Functional electrical stimulation, Exercise, Vascular adaptations, Intima media*
6 *thickness, Flow mediated dilatation*

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19 **Vascular adaptations in non-stimulated areas during hybrid cycling**
20 **or handcycling in people with a spinal cord injury: a pilot study of 10**
21 **cases**

Abstract

Study Design Sub-study of a randomized controlled trial

Objectives To examine if hybrid cycling (cycling with the legs via electrical stimulation combined with voluntary handcycling) compared to handcycling leads to different systemic vascular adaptations in individuals with a long-term spinal cord injury (SCI) .

Setting Two rehabilitation centers in the Netherlands.

Methods Ten individuals with a SCI trained on a hybrid bicycle (N=5) or a handcycle (N=5) for 16 weeks twice a week. Prior to and following the training the intima media thickness (IMT) of the common coronary artery (CCA) and superficial femoral artery (SFA) were measured and the flow-mediated dilation (FMD) of the brachial artery (BA) was analyzed.

Results Before training, there were no significant differences in any of the outcome measures between the groups. We found no change in CCA-IMT (pre: 0.616mm, post: 0.586mm), or in SFA (pre: 0.512mm, post: 0.520mm) after hybrid cycling. We also found no change in FMD % of BA after hybrid cycling (pre: 9.040%, post: 9.220%). There were no changes in CCA-IMT, SFA-IMT and FMD% after handcycling either.

Conclusions It appears that 16 weeks of twice weekly training of up to 30 min on a hybrid bicycle or handcycle does not lead to systemic vascular adaptations. A larger sample size and training protocol with more frequent and higher intensity training (which might involve a home-based setting and an adapted period prior to the training) might show different results.

22 **Introduction**

23 Provision of interventions that improve vascular adaptation are highly relevant given the high mortality and
24 morbidity of cardiovascular disease (CVD) and cerebrovascular disease, particularly among individuals with

25 spinal cord injury (SCI). The prevalence of cardiovascular disease is 17% in people with a SCI compared to 5% in
26 individuals without a SCI (1) (2) (3). It is known that exercise plays an important and relevant role in vascular
27 adaptations.

28 One way to measure vascular adaptations is through the intima media thickness (IMT), another is through flow
29 mediated dilation (FMD) with cuff inflation and deflation. In the case of able-bodied people with increased
30 cardiovascular risk or disease demonstrating a priori impaired FMD, exercise training leads to improvement in
31 FMD. In healthy able-bodied people a temporary increase in FMD with normalization is expected after a period
32 of training. Existing research recognizes the critical role played by exercise in able-bodied people on activated
33 and non-activated regions (9) (10). Exercise three times a week of 30 minutes of cycling for 8 weeks resulted in
34 a decrease of wall thickness and Wall-to-Lumen ratio in the superficial femoral artery and the carotid artery
35 (11). A study focusing on training for the marathon (4 times a week for a period of 16 weeks) showed a
36 decrease in brachial and popliteal total wall thickness and increase in lumen diameters (12). A six-month
37 training program consisting of either full body resistance training or endurance training showed a decrease in
38 carotid artery intima media thickness (IMT)(13).

39 In people with SCI, hybrid cycling, which includes cycling with the legs via electrical stimulation (ES) combined
40 with voluntary handcycling, is the approach with the most potential for improving the endothelial function in
41 the activated limbs of people with a SCI (6). In people with SCI, despite the increased cardiovascular risk, FMD is
42 higher than in healthy people but FMD decreases in the stimulated areas following a period of exercise training
43 (4)(5) (17). Previous studies in people with SCI (7) (14) (15) (8) have only shown local vascular adaptations after
44 a period of ES exercise, but not in the non-stimulated areas. Thijssen et al. (8) found that local vascular
45 adaptations (diameter) occurred in the ES- stimulated areas, but not in the non-stimulated areas (calf and
46 forearm) (diameter and FMD), in individuals with a SCI after 4 weeks of hybrid cycling (3 times a week for 30
47 minutes). Measurements on the forearm, however, were biased by the fact that the arms were highly
48 developed as a result of regular wheelchair exercise. In addition to that, this study was limited to a period of 4
49 weeks of hybrid cycling, which was probably not sufficient for vascular adaptations in the non-stimulated areas.
50 It has previously been observed that the systemic effects of hybrid cycling result in increased cardiorespiratory
51 fitness in people with a SCI . It was also demonstrated that hybrid cycling resulted in a higher metabolic rate
52 and cardiorespiratory response than handcycling (16).

53 It is established that exercise in people with a SCI induces vascular adaptation in the stimulated area. The
54 influence of exercise on the non-stimulated areas, however, remains unclear. To date no study has investigated
55 the effect of exercise for periods longer than 4 weeks on the non-stimulated areas in persons with a SCI.

56 The aim of this pilot study was to explore whether vascular adaptations occur in the non-activated areas after a
57 relatively long training period either with hybrid cycling or handcycling. The IMT and diameter at the common
58 coronary artery (CCA) and superficial femoral artery (SFA) were used to measure non-stimulated areas. FMD at
59 the brachial artery (BA) was a measure for non-stimulated areas in de hybrid group with the consideration of
60 local muscle activity during hand and hybrid cycling. It was expected that training would reduce the intima
61 media thickness (IMT) in the CCA and SFA. It was also expected that the difference in mainly the CCA and SFA
62 would be larger with hybrid cycling compared to handcycling, due to the larger muscle mass involved.

63

64 **Methods**

65 This study is part of a larger study, which was described by Bakkum et al.(18) in 2013. Briefly, a 16-week
66 Randomized Controlled Trial was performed in two Dutch rehabilitation centers (Amsterdam and Nijmegen)
67 between November 2011 and November 2013. Participants were randomly assigned to either the experimental
68 group (hybrid cycle training group) or the control group (handcycle training group). Participants in Nijmegen
69 also provided vascular measurements as part of the present study in order to study vascular adaptations in
70 non-stimulated areas during hybrid cycling as opposed to handcycling.

71

72 **Participants**

73 Ten man with a long-standing SCI of at least 8 years, aged between 28 and 65, wheelchair dependent and
74 inactive (lower than the 75th percentile in the Physical Activities Scale for Individuals with Physical Disabilities
75 (PASIPD)(19) of a Dutch cohort study population) were recruited from the database of the rehabilitation center
76 in Nijmegen. Each received an information letter and signed an informed consent indicating voluntary
77 participation in the study. The study was completed in accordance with the Medical Ethics Committee of the
78 VU University Medical Centre Amsterdam. After screening by a rehabilitation physiatrist, patients with pressure
79 sores, cardiovascular problems, severe musculoskeletal complaints or psychiatric problems were excluded.

80

81 ***The handcycle***

82 The handcycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany) was equipped with a wide synchronous
83 bull-horn crank, and with 8 gears that can be changed manually. The handcycle was placed on a Tacx Flow
84 ergotrainer (Tacx Flow, Technische Industrie, Tacx B.V., Wassenaar, The Netherlands).

85

86 ***The hybrid cycle***

87 The BerkelBike Pro (Berkelbike BV, Sint-Michielsgestel, the Netherlands) with a similar handbike and also
88 placed on the Tacx Flow ergotrainer was used for hybrid cycling, combining synchronous handcycling with
89 asynchronous ES-induced leg cycling. A 6-channel stimulator (NeuroPro, Berkelbike) provided ES via self-
90 adhesive 50 x 90 mm surface electrodes placed bilaterally over the quadriceps, hamstrings, and gluteal
91 muscles. The pulse duration was 400 μ s and maximum current amplitude was 150mA.

92

93 ***Training protocol***

94 One week before the first training session, participants carried out a graded peak exercise test in their own
95 handrim-propelled wheelchair and had their maximal exercise response measured. Participants performed 32
96 training sessions within a continuous period of 16 weeks. Each training session started with a warm-up,
97 followed by a training session of between 18 and 32 minutes (rate of perceived exertion of 4-7 on the Borg's 10
98 point scale and 65-75% heart rate reserve response during training). For the detailed training program see
99 Bakkum et al. (18).

100

101 ***Outcome measurement***

102 The primary outcomes were intima media thickness (IMT) at the carotid artery and FMD at the brachial artery.

103 Secondary outcomes were IMT and FMD at the femoral artery.

104 At baseline (pre-test) we collected patient characteristics: age, gender, lesion level and completeness with the
105 AIS scale, medical history, intoxication history, spasticity, body mass, height, body mass index (BMI) and PASIPD
106 score (Physical Activities Scale for Individuals with Physical Disabilities) (19). The IMT and diameter were
107 measured at CCA, BA and SFA and FMD at BA was measured. During the training we collected training time,

108 stimulation (amplitude) of the ES, Borg scale and if there was any discomfort or pain. After the training
109 program (post-test) IMT, diameter and FMD were measured again as soon as possible.

110 *Intima media thickness (IMT) and diameter* were measured under standardized conditions using high resolution
111 ultrasound (T3000, Terason, Burlington, MA) across arteries in the neck (common carotid artery) and leg
112 (superficial femoral artery). With the AVI converter the files were converted to Dicom files. Those files were
113 analyzed in IMT software version 3.0. The program visualized the upper and lower lumen intima and the media
114 adventitia (figure 1). Frames that were taken when the ultrasound was moved, frames where no media
115 adventitia was found, and part of the frames where no media adventitia was found or placed wrong, were
116 excluded. Then the program made a calculation of the mean, minimum, maximum, and standard deviation of
117 the IMT and Diameter. The analysis was done by a different person than who performed the ultrasound
118 measurement and was blinded for the training group. To gain experience with the computer program all 10
119 analyses were done once without adding those results into the study result. When all measurements were
120 done a second time, the analyses were viewed together with an expert and after receiving advice the analyses
121 were done a third time. Those results were used in the study results.

122

123 *Flow mediated dilatation and nitroglycerine mediated dilatation* were measured under standardized conditions
124 using high resolution ultrasound across arteries in the arm (brachial artery) and leg (superficial femoral artery).
125 The video was analyzed in Dicom encoder and FMD/blood flow analysis program version 3.0. The region of
126 interest in the Doppler signal and in the artery were selected. The video was played while the artery and
127 Doppler signal were visualized. The program transfers this into graphs; one with time on the x-as and diameter
128 on the y-as, one with peak blood flow on the x-as and one with shear rate on the y-as. The peak blood flow
129 graph is to inform when the constriction and dilatation took place. Irregularities of the signal were selected and
130 the video of that part was shown again. If at that moment the ultrasound was moved, those areas were
131 excluded. In FMD settings the baseline area and dilatation area were selected and subsequently the program
132 calculated baseline diameter, FMD peak diameter, FMD peak diameter percentage. The same was done with
133 glyceryl trinitrate (GTN) mediated dilatation with GTN settings, where baseline, GTN peak, GTN peak
134 percentage were measured. Again to gain experience all measurements were done three times and viewed
135 with an expert, where only the third results were used for further analysis.

136

137 **Statistical analysis**

138 Statistical analysis was performed using the SPSS statistical software package version 23. The repeated
139 measures ANOVA analysis was used and effect size (Cohen's d) to examine the effect of 16 weeks exercise
140 either with hybrid cycling or handcycling on IMT and FMD of the different arteries. The handcycle and hybrid
141 cycle training group were equally analyzed. For Cohen's d 0.2 is a small effect, 0.5 medium and 0.8 large (20).
142 To analyze the individual effects, graphs were made with the pre-test outcomes of IMT, diameter and FMD
143 plotted against the post-test outcomes.

144

145 **Results**

146 *Participants*

147 Characteristics of the participants are shown in Table 1. Participants 5, 9 and 10 were smokers and participants
148 3, 4 and 5 had mild spasticity. All 10 participants finished the study but participant 8 missed one training
149 session, participant 7 missed two sessions and participant 10 missed five sessions due to holidays. With
150 participant 1 some measurements were incorrect. Participant 6 was too hypotensive post-test to complete the
151 measurements. Half the participants (participants 3,6,7,8 and 10) were measured more than one week after
152 the last training session.

153

154 *Vascular adaptations*

155 In the whole test group (hybrid and/or handcycle) thirty-two handcycle or hybrid cycle training sessions did not
156 result in significant changes in IMT in the CCA and in the SFA. No changes in diameter and FMD of the BA (table
157 2 and figure 2) were found. When viewing the plots in which the individual pre- and post-test outcomes are
158 visualized, group differences are not clearly shown and contradictory results between the individual
159 participants appeared.

160

161 **Discussion**

162 The study showed that 16 weeks (twice a week for 18-30 minutes) of hybrid cycling or handcycling did not

163 result in vascular changes at non-stimulated areas. Our hypothesis was that after hybrid cycling or handcycling
164 IMT at the non-stimulated area's would get smaller but neither on a group level, nor on an individual level were
165 vascular changes found.

166 Pre-test results showed that the diameters of SFA and CCA were comparable to those previously reported (5)
167 but the pre-test FMD was slightly higher (4)(21). People with SCI use their arms more intensively than able-
168 bodied people, which might show a local trained effect of the arm. Pre-test results of the 3 participants who
169 smoke, were the same as the rest of the group, even though it is known that there is an inverse relationship
170 between the intensity of tobacco smoke and FMD (2). Pre-test results of the 3 participants with mild spasticity
171 were the same as the rest of the group even though spasticity can simulate a small exercise effect. Two people
172 with a cervical lesion (participant 3 and 5) were included, which could have influenced their FMD in the brachial
173 artery with a larger pre-test FMD (due to atrophy of the arm muscles). They did, however, not show different
174 values in their pre-test FMD (perhaps because one had a motor incomplete lesion and both had spasticity).

175 The 16 weeks, twice a week, up to 30 minutes, hybrid or handcycle training program did not result in any
176 vascular adaptations of non-stimulated areas in people with a SCI. All except one participant finished their
177 exercise schedule. Results contrast with several training studies (including able-bodied people) in which the
178 training frequency was at least 3 times a week resulting in vascular changes in non-trained areas (13)(22).

179 Thijssen et al. (8) did not measure any change in vascular adaptation in the brachial artery in patients with SCI
180 after 4 weeks of twice weekly hybrid cycling for 25 minutes. Four weeks of hybrid cycling, and 16 weeks of
181 twice a week 30 min training might, therefore, not have been long and/or frequent enough for vascular
182 adaptation. To train for a 3 month period 3x/week for 60 minutes will be a challenge for this group. If people
183 with a SCI want to achieve the benefits, lifelong training will probably be necessary to reduce their increased
184 risk of cardiovascular diseases. It is a challenge to arrange frequent long-term training in a rehabilitation centre
185 with enough motivated sedentary participants. Training at home with a handcycle and Complex electrical
186 stimulation might be an acceptable alternative.

187 The training intensity in our study was between 4-7 on the Borg's 10 point perceived exertion scale and/or 65-
188 75% heart rate reserve response during training. In our study the time and intensity were gradually increased,
189 whilst all the studies with able-bodied participants immediately started with training at least 3 times a week.
190 People with a SCI need to gradually increase the intensity to adapt to hybrid cycling. It is known that exercise
191 intensity is an important factor in remodelling endothelial function in healthy, obese and heart failure patients

192 (23) (24)(25). Training at a higher intensity might have been more effective in people with SCI. To achieve a
193 higher intensity, one may increase the resistance with handcycling. However starting on a high intensity is
194 prone for overuse injuries. Especially in case of spinal cord injured people, who are limited in which muscles
195 they can use . Adding more resistance might make the exercise more prone to overuse injuries in the arms,
196 which can be a significant handicap for wheelchair users with SCI (29). The balance between exercise with high
197 intensity and low risk of overuse is important. It might be necessary to separate the adapting period from the
198 intervention period and to start the actual intervention after the adapting period, resulting in a longer period of
199 exercise with a high intensity.

200 The limitations of our study include the small sample size and the heterogeneity within the sample. We were
201 aware that it would be difficult to get significant results with such a small sample size in this pilot study, but we
202 hoped to see a trend, which could be explored in a future study. Our recommendation for a future study would
203 be more frequent training (>3 times a week) with a higher intensity in a home-based setting with an adaptation
204 period prior to training.

205

206 **Conclusion**

207 Sixteen weeks of hybrid cycling or handcycling did not result in vascular adaptation in non-stimulated areas
208 (such as brachial, coronary artery and femoral superficialis artery). We cannot conclude that this does not
209 happen either with a more intense and frequent training protocol with a larger sample size. This pilot study had
210 its limitations, particularly the small sample size. To analyse if hybrid cycling or handcycling has an effect on the
211 non-stimulated areas, a study design with more frequent training and higher intensity is needed, which might
212 involve home-based training and an adaption period prior to training.

213

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216

217 **Conflict of interest**

218 All authors have nothing to disclose.

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Table 1. Patient information

* ASIA grade is used to classify the completeness of the lesion: A, sensory and motor complete; B, sensory incomplete but motor complete; C, sensory and motor incomplete but no functional motor activity.

BMI = Body Mass Index, HB = handcycling, HC = hybrid cycling

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Table 2. Pre and post 16-week training values for the total group as well as hybrid cycle group and handcycle group, are provided for all outcome measures. For all outcome measures, no significant effects were found.

CCA: common coronary artery; IMT: intima media thickness; SFA: superficial femoral artery; FMD: flow mediated dilatation; BA: brachial artery; GTN: glyceryl trinitrate

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294

Figure 1: The carotid artery where the lumen intima (yellow) and media adventitia (red) are marked.

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Figure 2. A) scatter plot of the IMT at CCA, B) scatter plot of the diameter at CCA, C) scatter plot of IMT at SFA, D) scatter plot of diameter at SFA, E) scatter plot of FMD peak at BA and F) scatter plot of the percentage of FMD of the baseline at BA.

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300

301 **Table 1**

Participant	Age at time of inclusion (years)	Gender	Lesion level	ASIA Grade *	Time since injury (years)	BMI (kg/m ²)	PASIPD score (METS)	Group
1	64	M	T4	A	18	26.5	2.8	HC
2	30	M	T4	A	12	24.4	16.7	HB
3	47	M	C6	C	13	26.5	1.0	HB
4	45	M	T5	A	16	24.8	14.8	HB

5	38	M	C5	B	13	24.9	1.8	HC
6	49	M	T1	A	28	19.4	20.9	HC
7	31	M	T10	A	14	24.6	6.0	HC
8	58	M	T8	A	25	28.1	8.2	HC
9	45	M	T11	A	16	16.8	7.4	HB
10	38	M	T9	A	10	20.2	23.2	HB

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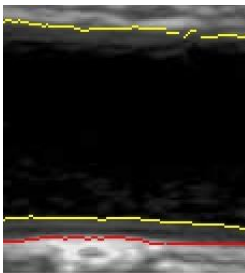
314 **Table 2**

	Total group					Hybrid cycling					Handcycling					Ptime	Ptime x group
	N	pre	post	Δ (SD)	d	N	pre	post	Δ (SD)	d	N	pre	post	Δ (SD)	d		
	Mean (SD)	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)	Mean (SD)			Mean (SD)						
CCA IMT (mm)	8	0.62 (0.13)	0.58 (0.08)	0.03 (0.15)	0.211	3	0.613 (0.11)	0.59 (0.05)	0.03 (0.10)	0.261	5	0.62 (0.16)	0.58 (0.11)	0.03 (0.18)	0.187	0.622	0.951

CCA diameter (mm)	9	6.8 (0.5)	6.7 (0.6)	0.07 (0.5)	0.139	4	6.9 (0.6)	6.5 (0.6)	0.34 (0.5)	0.066	5	6.7 (0.4)	6.9 (0.5)	-0.16 (0.30)	- 0.513	0.524	0.113
SFA IMT (mm)	8	0.54 (0.09)	0.56 (0.1)	-0.02 (-0.05)	- 0.477	4	0.54 (0.09)	0.61 (0.09)	-0.03 (0.05)	- 0.628	4	0.51 (0.06)	0.52 (0.09)	- 0.013 (0.05)	- 0.276	0.250	0.640
SFA diameter (mm)	9	5.8 (0.6)	6.0 (0.8)	-0.13 (0.63)	- 0.200	4	5.7 (0.8)	5.5 (0.7)	0.10 (0.08)	1.278	5	5.9 (0.4)	6.3 (0.7)	-0.38 (0.77)	- 0.492	0.650	0.192
Baseline prior to FMD measurement (mm)	9	3.99 (0.64)	4.11 (0.75)			4	4.14 (0.89)	4.11 (0.91)			5	3.87 (0.44)	4.11 (0.70)				
FMD peak BA (mm)	8	4.44 (0.66)	4.57 (0.70)	-0.13 (0.88)	- 0.147	3	4.81 (0.67)	4.73 (0.80)	0.07 (0.22)	0.325	5	4.24 (0.61)	4.46 (0.07)	-0.25 (0.10)	- 0.219	0.802	0.657
FMD % BA	8	8.94 (4.72)	8.88 (3.60)	0.07 (2.25)	0.029	3	9.5 (6.8)	9.2 (5.7)	0.23 (1.32)	0.175	5	8.6 (3.9)	8.7 (2.6)	-0.03 (2.83)	- 0.011	0.915	0.887
GTN peak (mm)	8	4.96 (0.82)	4.96 (0.63)	0.001 (0.78)	- 0.002	3	0.54 (0.08)	0.53 (0.08)	0.01 (0.2)	0.732	5	0.47 (0.07)	0.48 (0.05)	- 0.007 (0.10)	0.071	0.944	0.767
GTN %	8	22.1 (7.36)	22.9 (8.29)	-0.73 (5.10)	0.141	3	24.3 (7.8)	24.5 (10.4)	-0.21 (5.21)	- 0.040	5	20.9 (7.7)	21.9 (7.9)	-1.05 (5.62)	- 0.187	0.764	0.841

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316 **Figure 1**



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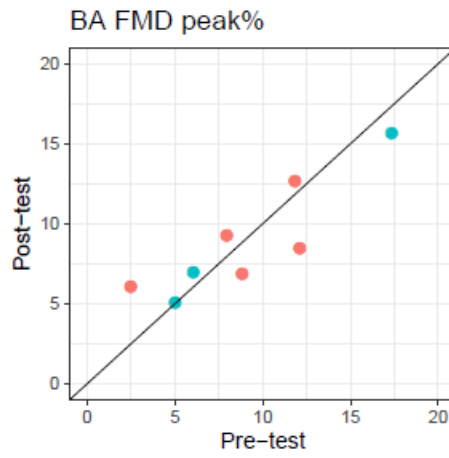
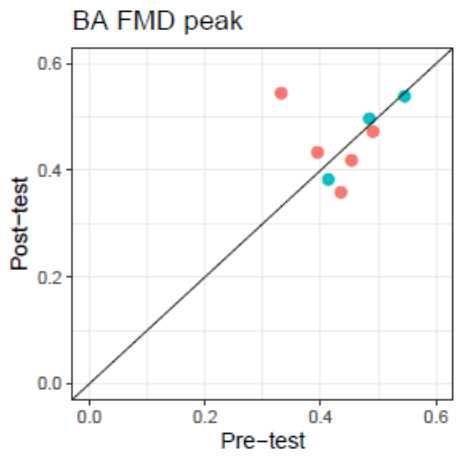
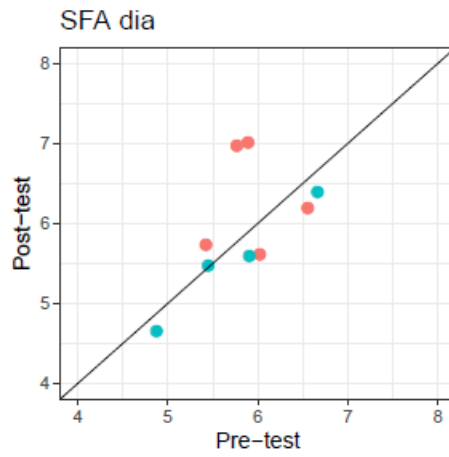
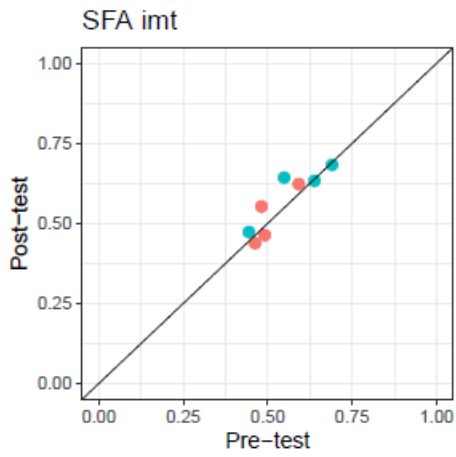
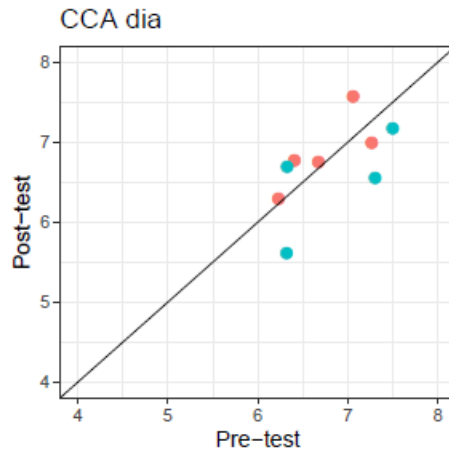
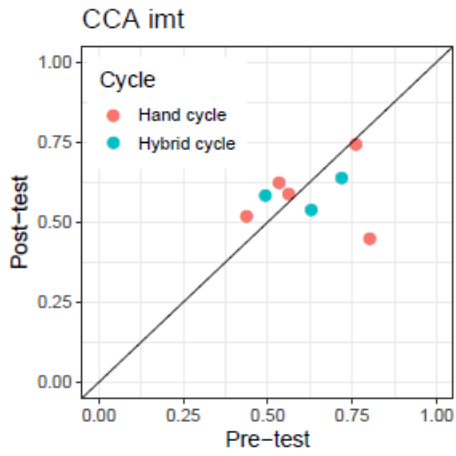
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325 **Figure 2**



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