

## **Exergaming Improves Older Adult Cognition: A Cluster Randomized Clinical Trial**

Cay Anderson-Hanley, PhD<sup>1,2</sup>, Paul J. Arciero, DPE, FACSM<sup>2,1</sup>, Adam

M. Brickman, PhD<sup>3</sup>, Joseph P. Nimon, BS<sup>1</sup>, Naoko Okuma, BS<sup>2</sup>, Sarah

C. Westen, BS<sup>1</sup>, Molly E. Merz, BS<sup>1</sup>, Brandt D. Pence, BA<sup>4</sup>,

Jeffrey A. Woods, PhD, FACSM<sup>4</sup>, Arthur F. Kramer, PhD<sup>5</sup>, and Earl A. Zimmerman, MD<sup>6</sup>

- 1 Healthy Aging and Neuropsychology Lab, Department of Psychology, Union College, Schenectady, NY
- 2 Health and Exercise Sciences Department, Skidmore College, Saratoga Springs, NY
- 3 Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY
- 4 Department of Kinesiology, University of Illinois, Urbana-Champaign, IL
- 5 Director of the Beckman Institute for Advanced Science and Technology, University of Illinois, Urbana-Champaign, IL
- 6 Director of the Alzheimer's Center of Albany Medical Center, Department of Neurology, Albany Medical Center, Albany, NY

**Corresponding author:** Cay Anderson-Hanley, PhD, Department of Psychology, Union College, 807 Union Street, Schenectady, NY 12308; ph: 518-388-6355; fax: 518-388-6177; email: andersoc@union.edu.

**Running Head:** Cybercycling for Cognitive Health

Text: 3,965 words; Number pages: 26 (with Tables and Figures); Tables 3; Figures: 2; Supplemental Files: (2 Figures, 5 Tables, 3 Text)

**Conflict of Interest:** The study was funded by a grant from the Robert Wood Johnson Foundation, Pioneer Portfolio: Health Games Research (#64449). No financial conflict of interest disclosures were reported by the authors of this paper.

**Abstract** (299 words)

**Background:** Dementia cases around the world are expected to reach 100 million by 2050, and thus calls are increasing for interventions to curb or prevent cognitive decline. Exercise yields cognitive benefits, but few older adults exercise. Virtual reality-enhanced exercise or “exergames” may elicit greater effort and greater cognitive benefit.

**Purpose:** To evaluate the following hypotheses: 1) exercise on a stationary bike with virtual reality tours and competition (“cybercycle”) will enhance executive function and clinical status more than a traditional stationary bike; 2) exercise effort will explain improvement; 3) brain-derived neurotrophic growth factor (BDNF) will increase and provide evidence of neuroplasticity.

**Design:** Multi-site cluster randomized clinical trial of the impact of three months of cybercycling vs. traditional exercise, on cognitive function in older adults. Data collected: 2008-2010; analyses conducted: 2010-2011.

**Setting/Participants:** 102 older adults from in eight retirement communities enrolled (ages ranged 58-99); 79 randomized; 63 completed.

**Intervention:** A recumbent stationary ergometer was utilized in both conditions. Virtual reality tours and interactive competitors were enabled on the cybercycle.

**Main Outcome Measures:** Pre and post measures included: executive function (Color Trails Difference, Stroop C, Digits Backwards); clinical status (mild cognitive impairment; MCI); exercise effort/fitness; and plasma BDNF.

**Results:** Intent-to-treat analyses, controlling for age, education, and clusters, yielded significant group x time interactions for composite executive function ( $p=.002$ ). A medium effect of cybercycling over traditional exercise was found ( $d=.50$ ). Cybercycling yielded 23% relative risk reduction in clinical progression to MCI. Exercise effort and fitness were comparable, suggesting another mechanism links cybercycling to cognitive benefit. A significant group x time interaction for BDNF ( $p=.05$ ) indicated enhanced neuroplasticity among cybercyclists.

**Conclusions:** Cybercycling older adults achieved better cognitive function than traditional exercisers, for the same effort, suggesting that simultaneous cognitive and physical exercise has greater potential for preventing cognitive decline.

**Trial Registration:** [www.clinicaltrials.gov](http://www.clinicaltrials.gov) Identifier: NCT01167400

## 1 **Introduction**

2 Dementia is a growing global epidemic with significant personal, social and economic  
3 costs<sup>1</sup> and has led to calls for interventions to prevent or slow cognitive decline.<sup>2,3</sup> Cross-  
4 sectional research suggests physical exercise may prevent or delay dementia,<sup>4-6</sup> and meta-  
5 analyses demonstrate that physical exercise improves cognitive function in normal aging<sup>7,8</sup> and  
6 in dementia.<sup>9</sup> Recent research has extended these findings to older adults with mild cognitive  
7 impairment<sup>10-12</sup> whose deficits are beyond those expected for their age, but which do not  
8 interfere with daily living and yet may be a precursor to dementia. Furthermore, evidence is  
9 accumulating that cognitive benefits may be achieved by way of improved neuronal functions,  
10 including neurogenesis, shown by concomitant structural and functional changes in the brain,<sup>13-17</sup>  
11 impacts on biomarkers of Alzheimer's disease,<sup>18-19</sup> and increases in brain-derived neurotrophic  
12 growth factor (BDNF).<sup>10,14,19,20</sup> Cognitive benefit from exercise is found primarily in executive  
13 control and frontal lobe functions, such as planning, divided attention, and inhibition  
14 responses.<sup>8,21,22</sup> These abilities are often impaired by dementia and are key to maintaining  
15 independence and delaying institutionalization.

16 The demonstrated cognitive and health benefits of exercise are such that the American  
17 College of Sports Medicine (ACSM) and the American Heart Association (AHA) upgraded  
18 recommended daily exercise.<sup>23</sup> Yet data from the CDC Healthy People 2010 Database indicate  
19 that only 14% of adults 65-74 years old and 7% of those over age 75 reported regular exercise.  
20 Physician prescription of exercise<sup>24</sup> has not been shown to substantially increase participation;  
21 less than 4% of patients in one study complied.<sup>25</sup> These data suggest the need for more  
22 compelling interventions to increase the motivation of older adults to exercise, as well as  
23 multimodal interventions that address the multiple deficits from physical inactivity.<sup>26</sup>

24 Virtual reality-enhanced exercise or “exergames” combine physical exercise with  
25 computer simulated environments and interactive videogame features, and have become popular  
26 as a means to promote healthy behaviors<sup>27</sup> and increase the appeal of exercise (e.g., the Wii Fit  
27 and PlayStation Move).<sup>28</sup> Exergames have the potential to increase exercise by shifting attention  
28 away from aversive aspects and towards motivating features such as competition and three-  
29 dimensional (3D) scenery. Participation in exergaming compared with traditional exercise can  
30 lead to greater frequency and intensity,<sup>29</sup> and enhanced health outcomes.<sup>28,30,31</sup> A recent study  
31 reported that compared with traditional stationary cycling, older adults preferred cycling with  
32 interactive gaming.<sup>32</sup>

33 Although promising, there are limited published data on whether interactive exergaming  
34 technologies are reliably associated with enhanced physical and cognitive health outcomes, and  
35 more controlled research on the effects of health games is needed.<sup>27,33</sup> One early study<sup>34</sup>  
36 investigated virtual reality-enhanced stationary cycling using virtual tours and on-screen  
37 competition, we refer to as “cybercycling,” and found cognitive improvement in patients with  
38 traumatic brain injury. However, without a traditional exercise control group, it is unclear  
39 whether cybercycling yielded cognitive benefit beyond physical exercise alone. While there are  
40 reports of the psychological benefits of cybercycling,<sup>29,30,35</sup> no previous randomized controlled  
41 trial has evaluated the cognitive benefits of virtual reality-enhanced exercise. Presented herein  
42 are results of the Cybercycle Study, a multi-site cluster randomized clinical trial in which the  
43 cognitive benefit of cybercycling was compared with traditional stationary cycling, for  
44 independent living older adults. Based on prior research showing primarily executive function  
45 gains from exercise,<sup>8,21,22</sup> it was hypothesized that cybercycling would yield greater executive  
46 function. Further, it was hypothesized that any change would be due to increased exercise effort

47 spurred on by engaging interactive virtual tours, competition and added mental challenge.  
48 Secondary analyses examined change in BDNF as a biomarker indicating possible  
49 neuroplasticity which has been implicated as a mechanism of change linking exercise to  
50 cognition.<sup>10,14,18-20</sup>

## 51 **Methods**

### 52 **Design**

53 This randomized clinical trial (2008-2010) compared the impact on executive function of two  
54 exercise interventions: physical exercise alone and physical plus mental challenge as combined  
55 in an exergame.

### 56 **Setting and Participants**

57 Participants were recruited by fliers and information sessions at eight independent living  
58 facilities. The facilities were chosen because of proximity to investigator institutions, similarity  
59 in size (average 100-200 residents), and presence of contiguous living areas to ensure indoor  
60 access to a study bike (to minimize barriers associated with travel). Participants volunteered  
61 based on demonstrations of cybercycle functionality, not knowing which condition they would  
62 be randomized to, but aware that all could use the cybercycle after the three-month intervention.  
63 Volunteers aged 55 years or older were screened; exclusion criteria were known neurological  
64 disorders (e. g., Alzheimer's or Parkinson's) and functional disabilities that would significantly  
65 restrict participation in cognitive testing or exercise. Written physician approval was required.  
66 Union and Skidmore Colleges' institutional review boards approved the study; participants  
67 provided written informed consent. The study was registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
68 (NCT01167400). A priori sample size estimates were calculated based on published effect sizes  
69 for cognitive ( $d=.48$ )<sup>8</sup> and physiological ( $d=.41$ )<sup>36</sup> outcomes from physical exercise. An a priori

70 power analysis had found that in a 2 x 2 (group x time) design, a sample of 100 would achieve  
71 .82 power to detect a significant effect ( $p=.05$ ). At the time of study design when obtaining  
72 funding, individual randomization was planned and the need for cluster randomization was not  
73 foreseen; actual post hoc power is reported below in Results).

#### 74 **Interventions**

75 Participants in the cybercycle and control conditions rode identical recumbent stationary  
76 bikes, except for the virtual reality display that was enabled on the cybercycle (Suppl. Figure 1  
77 and TextFile1). Participants were trained in the use of the bike, log-in procedures, and paper log  
78 for recording ride statistics as a back-up to the computer. Participants were given a target HR  
79 range to maintain during exercise using the Heart Rate Reserve (HRR) method;<sup>23</sup> mid-  
80 intervention adjustments were made to maintain a relative HRR of 60%. A one-month  
81 familiarization period allowed participants to learn to attend to continuous biofeedback  
82 information for safety (e.g., HR), before introducing distracting virtual tours in the cybercycle  
83 condition. Participants were instructed to gradually increase exercise frequency to 45 minutes per  
84 session, five times per week consistent with the ACSM and AHA recommendations.<sup>23</sup> Individual  
85 progress reports and leaderboards were posted weekly to control goal-setting and competition  
86 across interventions. Participants were asked to hold constant other lifestyle factors (e.g., diet  
87 and other physical activity) during their study participation to isolate the effect of the  
88 interventions. The minimum threshold for “completers” was 25 rides during the intervention  
89 period; thus “completers” rode an average of three rides per week minus two weeks allowance  
90 for illness, holidays, or equipment repair.

91            **Cybercycle Group.** After one month of familiarization, cybercycle participants  
92 experienced 3D tours and competed with their own “ghost” rider (last best ride). During month  
93 three, participants were instructed to outpace on-screen riders.

94            **Control Group.** After one month of familiarization, controls continued to ride the  
95 traditional stationary bike viewing biofeedback information (e.g., HR and mileage). Each month,  
96 placebo training (e.g., hydration and stretching) matched the attention given to the cybercycle  
97 group.

98            **Randomization.** A priori plans were for individual random assignment through software  
99 controls, but equipment problems, combined with limited funding and space, led to cluster  
100 assignment to control cross-condition contamination. Sites were selected by random draw.  
101 Cluster random assignment achieved similar levels of cognitive function and physiological status  
102 at pre-test, although the groups differed in age and education which were entered as covariates in  
103 analyses ( $p=.002$  and  $p < .001$ , respectively; Table 1).

#### 104 **Main Outcome Measures**

##### 105 ***Cognitive Assessment***

106 Cognitive testing was done at enrollment (baseline), one month later (pre-intervention), and three  
107 months later (post-intervention). Analyses were conducted using pre- and post-scores. Baseline  
108 testing minimized the impact of practice and learning effects associated with serial assessments  
109 and provided a more stringent test of the main hypothesis.<sup>38</sup> Blinded ratings were achieved in  
110 most cases. The primary cognitive outcome of interest, executive function, was assessed via  
111 Color Trails 2-1 difference score (time to connect alternating color and number dots, minus time  
112 to connect only numbered dots),<sup>39</sup> Stroop C (time to name color of ink of contrasting color  
113 word),<sup>40</sup> and Digit Span Backwards (number of correct trials repeating a string of numbers in

114 reverse order).<sup>41</sup> To reduce the number of statistical comparisons, an executive function  
115 composite score was obtained by converting raw scores on each test to Z-scores using the grand  
116 mean and standard deviation across both groups for each time point, then averaging the three  
117 measures (Cronbach 's  $\alpha = .67$ ). Timed tasks were reversed; a positive value on the composite  
118 indicates a score above the mean. Secondary cognitive outcomes were included to characterize  
119 the sample (e.g., clinical status below); no changes were expected on these tests (Suppl.  
120 TextFile2). At the completion of the study, participants' clinical status pre- and post-intervention  
121 was classified according to "typical" diagnostic criteria<sup>43,44</sup> for mild cognitive impairment (MCI;  
122 performance  $\leq 1.5 SD$  on at least one subtest in the domains of executive function, verbal  
123 fluency, verbal memory, visuospatial skill, and visuospatial memory compared to normative  
124 data).<sup>41</sup> MCI incidence was comparable with prior research (Table 1).<sup>45</sup>

### 125 *Physiological Assessment*

126 Baseline and post-exercise measurements included: weight (kg), height (cm), and Body Mass  
127 Index (BMI); total and abdominal body composition (fat and lean mass) using the iDXA (GE  
128 Lunar, Inc.), muscle strength of quadriceps and hamstrings using the HUMAC Cybex  
129 Dynamometer (CSMI Solutions, Inc.), and insulin and glucose (Millipore, Inc.).

### 130 *Assessment of Exercise Behavior*

131 During the first year, daily physical activity (kcal) was measured using the Aerobics Center  
132 Longitudinal Study Physical Activity Questionnaire (ACLS-PAQ).<sup>46</sup> Metabolic equivalents were  
133 used to compute energy expended in activities. In the second year, additional resources allowed  
134 measurement of daily physical activity (kcal) using an accelerometer (Actical; Phillips  
135 Respironics, Inc). Ride behaviors (frequency, intensity, and duration) were recorded on the bike  
136 computer and by participants in a paper log.



137 ***Neuroplasticity Assessment***

138 Fasting morning plasma samples were collected during pre- and post- evaluations, not after  
139 exercise. Brain-derived neurotrophic factor (BDNF) levels were analyzed via enzyme-linked  
140 immunosorbant assay (ELISA; Chemicon, Millipore, Billerica, MA; Suppl. TextFile2).

141 **Statistical Analysis**

142 Data were analyzed using SPSS v19.0 (Chicago, Illinois). For normally distributed continuous  
143 variables, arithmetic means and SDs were calculated. For comparisons between groups of  
144 categorical baseline data,  $\chi^2$  analyses were calculated. For comparisons of continuously  
145 distributed baseline and demographic variables, *t* tests were calculated. Intent-to-treat analysis  
146 was conducted using the last observation carried forward (LOCF). Four analytic strategies were  
147 employed to examine between-group changes in outcomes: intent-to-treat, complete-case, age-  
148 matched, and comparison of completers and non-completers.

149 Mixed linear modeling, including fixed and random effects, estimated the impact of the  
150 interventions on executive function composite scores, when adjusted for age, education, and  
151 nested variability in clusters (eight sites). A likelihood ratio test was conducted to compare the  
152 full and restricted models, with and without sites nested. Follow-up repeated measures general  
153 linear models (GLM) examined the group x time interaction effect, first by examining the  
154 multivariate omnibus test (to control Type I error), then examining the univariate results for the  
155 three executive function measures. To test whether between-group differences in cognitive  
156 outcomes were due to differential exercise effort, *t* tests were used. Effect sizes were computed  
157 using Cohen's *d* formula with pooled standard deviations. Tests of statistical significance used a  
158 two-sided alpha of  $p=.05$ .

159 **Results**

160 A CONSORT flow chart (Figure 1) shows 102 independent living, older adults from eight  
161 retirement communities met criteria and consented to participate; 79 began exercise training and  
162 were randomized by site (average cluster  $n=10$ ,  $SD=3.6$ ; Figure 1). Sixty-three older adults,  
163 ranging in age from 58 to 99, completed the study (80% of randomized).

#### 164 ***Effect of the Intervention on Cognitive Function, Physical Health and Exercise Behaviors***

165 The interaction x time effects of the full and restricted mixed linear models were highly  
166 similar ( $F[1,51.8]=10.4$ ,  $p=.002$ ;  $F[1,76.2]=10.4$ ,  $p=.002$ , with and without sites nested,  
167 respectively). There was no statistically significant benefit of adding the cluster random effect  
168 (LR  $\chi^2[1]=3.16$ ,  $p=.93$ ); thus, in order to maximize degrees of freedom in this relatively small  
169 sample, the least restrictive fitting model was selected and subsequent parsimonious analyses  
170 were chosen. A significant difference between groups in change in executive function over three  
171 months was indicated by a significant group x time interaction in a multivariate repeated  
172 measures GLM of Color Trails Difference, Stroop C, and Digits Backwards, simultaneously and  
173 revealing a large effect ( $F[3,62]=5.50$ ,  $p=.002$ ,  $\eta_p^2 = .21$ , power=.93). Given the significant  
174 omnibus test, univariate group x time interactions were examined and found significant for all  
175 three measures of executive function (Table 2).

176 Planned simple effects analyses controlled for age, education, and cognitive performance  
177 at baseline, and revealed a significant increase in performance on the Color Trails Difference  
178 ( $p=.01$ ) and Stroop C ( $p =.05$ ) tests for cybercyclists, with no change for controls. Cybercyclists  
179 maintained a steady performance on Digits Backward, whereas the control group declined ( $p$   
180  $=.01$ ). No significant interaction effects were found on physiological or secondary cognitive  
181 outcomes (Table 2). Analyses were repeated using age-matched and complete-case subsamples  
182 and results were similar (Suppl. Tables 1-4). No significant differences in exercise frequency,

183 intensity or duration were found between the cybercyclists and controls (Table 3). While the  
184 average energy expended was relatively low (approximately 100 calories/ride), research has  
185 shown that even low-intensity exercise (100 calories) can serve as an adequate training stimulus  
186 among sedentary older adults.<sup>47</sup>

187 Cybercycling yielded a medium average effect size for executive function over-and-  
188 above the average effect for traditional exercise ( $d=.50$ ), contrasted with prior research that  
189 showed a small effect size for aerobic exercise over-and-above non-aerobically exercising  
190 controls ( $d=[.48-.16]=.32$ ),<sup>52</sup> Cybercyclists experienced a 23% reduction in risk of clinical  
191 progression to MCI compared with traditional exercisers (9 controls versus 3 cybercyclists  
192 converted to MCI). That is, using the “typical” diagnostic criteria for MCI,<sup>43,44</sup> these participants  
193 began the trial with performances in the normal range, but experienced a decline to -1.5 SD  
194 below normative data on at least one test within those domains.

195 Adherence to prescribed exercise (79.7%) was comparable with prior research (78.2%).<sup>12</sup>  
196 Consistent with CONSORT standards, a comparison of study completers and non-completers is  
197 reported. Similar rates on non-completion were found in both conditions; at baseline, non-  
198 completers were more compromised than completers on some cognitive and physiological  
199 measures which may have led to greater difficulty completing the study (Suppl. Table 3).  
200 Supplemental Table 6 shows the 13 adverse events in the study.

#### 201 ***Biomarker Evidence of Possible Neuroplasticity: BDNF Results***

202 Plasma BDNF data from 30 participants were available (ages 66-89). A significant group (cycle  
203 condition) x time (pre and post-intervention) interaction, with age and education as covariates,  
204 was found revealing that cybercyclists experienced a greater increase in BDNF than traditional  
205 exercise (Suppl. Figure 1;  $F[1,25]=4.89$ ;  $p=.05$ ).

206 **Discussion**

207 Data from this cluster randomized clinical trial provide preliminary evidence that exergaming  
208 can yield greater cognitive benefit, buffering against decline, more so than traditional exercise  
209 alone. Independent living older adults who exercised on a virtual reality-enhanced cybercycle for  
210 three months, had significantly better executive function than those expending similar effort on a  
211 traditional stationary bike. In contrast with prior research showing a small effect of exercise  
212 over-and-above controls,<sup>8</sup> cybercycling produced a medium effect over-and-above traditional  
213 exercise, with average improvements in performance of half a standard deviation. Additionally,  
214 while needing replication in a larger sample, fewer cybercyclists converted to MCI, suggesting a  
215 reduction in risk of progression to MCI.

216 Contrary to expectations, effort and fitness did not appear to be the factors behind  
217 differential cognitive benefits found in the cybercycle group. There were no differences between  
218 the two groups on measures of exercise effort or physiological outcomes. Since this was a  
219 prescriptive intervention for both groups, and not a naturalistic study, it appears that participants  
220 in both groups were compliant with the regimen (similar goals were set and met), and further  
221 research is needed to evaluate whether naturalistic use would lead to greater effort by  
222 cybercyclists. These findings are consistent with some assertions in the literature that the  
223 cognitive benefit derived from exercise is not necessarily tied to fitness outcomes, although the  
224 debate continues.<sup>47,48</sup> Future research will be needed to tease apart the contributions of a variety  
225 of factors in the cybercycling condition. Consistency across conditions for goal setting and  
226 competition suggests virtual reality imagery and interactive decision-making might be the potent  
227 factors of the cybercycle. Exit interviews provided anecdotal evidence of the value of these  
228 unique features. Participants commented on their enjoyment of visual stimulation and the

229 challenge of outpacing avatars. One 86 year-old noted she felt healthier and attributed this to  
230 actively maneuvering to “compete with that fellow ahead of me!” A 92 year-old participant  
231 noted, “It’s fun to work with that screen and see the other bikers.” Cybercycling provides a  
232 different experience than other cognitive stimulation such as television, since cybercyclists are  
233 interactively engaged.

234 One explanation for the greater cognitive benefit found with cybercycling compared with  
235 traditional cycling could be that the effect is due directly to the added cognitive exercise required  
236 of the cybercycle. Given that both exercise intervention samples exerted similar effort over three  
237 months, the main difference between the two interventions was the virtual reality experience.  
238 Navigating a 3D landscape, anticipating turns and competing with others, requires additional  
239 focus, expanded divided attention, and enhanced decision-making. These are activities that  
240 depend in part upon on executive function, which was significantly affected. A direct impact of  
241 cognitive stimulation herein does resonate with a growing, but formative literature on the effects  
242 of cognitive training.<sup>49</sup> While research is mixed and transfer is debatable, some research supports  
243 the utility of cognitive exercise to facilitate cognitive health in older adults.<sup>50-53</sup> Future research  
244 should measure the amount of cognitive stimulation participants engage in during the period of  
245 an exercise intervention to clarify the potential added benefit of activities beyond physical  
246 exercise (e.g., videogames or book clubs).

247 Another explanation for the greater cognitive benefit found for cybercycling compared  
248 with traditional cycling could be that the effect is due to the *interactive* nature of combined  
249 physical and cognitive exercise. Perhaps cybercyclists benefit from a dual-exercise experience,  
250 accruing the positive effects of intertwined cognitive and physical exercise. When comparing  
251 average effect sizes in the literature,<sup>52</sup> controls demonstrate test-retest growth (.16), cognitive

252 stimulation alone yields a comparable negligible effect (.13), physical exercise yields a small  
253 effect over-and-above controls (.32), while combined cognitive and physical exercise herein  
254 produced a medium effect over-and-above traditionally-exercising controls (.50). It is interesting  
255 that the combined effect of cognitive and physical exercise exceeds the sum of effects noted in  
256 the literature above, perhaps indicating a compounding or synergistic effect of cybercycling.  
257 Future research could evaluate this by comparing cognitive stimulation alone, physical exercise  
258 alone, and the combination of the two, as in many exergames. The exergame utilized herein, may  
259 allow the mind to be engaged in an interactive way with the physical challenge, perhaps  
260 providing a unique mechanism that fosters added cognitive benefit. Compounding cognitive  
261 benefit from a combined task does fit with the evolving understanding of the mechanisms of  
262 brain plasticity and the role of exercise and enriched environments in inducing angiogenesis,  
263 neurogenesis and other changes that foster neurovascular integrity.<sup>15,54</sup> A combined effect would  
264 be consistent with the animal literature, where cognitive benefit from physical exercise and  
265 mental stimulation have been found to occur by different mechanisms (cell proliferation and cell  
266 survival, respectively).<sup>54-56</sup> This combined-effect hypothesis expands upon prior research in  
267 humans, which has found enhanced cognitive benefits of physical and cognitive exercise  
268 interventions administered in tandem.<sup>57-58</sup> Similarly, these findings fit with prior research that  
269 indicates cognitive benefit over and above traditional exercise, from physical exercise that is  
270 cognitively challenging (e.g., Tai Chi or dancing).<sup>59-61</sup> No previous research has examined the  
271 possibility of added cognitive benefit of simultaneous, interactive cognitive and physical exercise  
272 in a controlled trial, where the physical motions are the same, but the mental challenge is  
273 experimentally controlled.

274 To further illuminate possible mechanisms linking exercise to cognitive change,  
275 alternative measures of intermediary physiological or brain “fitness” (e.g., neurotrophic growth  
276 factors), may be needed beyond cardiovascular fitness outcomes typically assessed.<sup>62</sup> In this  
277 study, it was found that cybercyclists experienced a significantly greater increase in BDNF than  
278 traditional exercisers, suggesting exercise may lead to cognitive benefits in part by way of  
279 biomarkers linked to neurotrophic effects. The literature on BDNF change with physical exercise  
280 is mixed and researchers continue to evaluate possible moderators such as age, sex, and the type  
281 of exercise.<sup>10,14,20</sup> The fact that the cybercycle condition exhibited a significant change in BDNF,  
282 does fit with the hypothesis that the cognitive exercise component may have been a meaningful  
283 intermediate mechanism. These results resonate with prior research which has shown a  
284 significant increase in BDNF after computerized cognitive training.<sup>63</sup>

285 Compared with prior research on the effects of physical exercise alone, the effect of the  
286 cybercycle intervention adds to the growing consensus that exercise has a consistent effect on  
287 executive functions.<sup>8,21,22</sup> However, the control group herein was also an exercising group  
288 (consistent with recommendations),<sup>64</sup> but did not show pre- to post-test improvement on  
289 executive function. It appears the added rigor of using an additional pre-test for familiarization  
290 did “wash-out” practice advantages<sup>38</sup> evident in prior studies. Traditional exercise may have  
291 slowed decline, consistent with some prior research which found that in a similar aged sample,  
292 the control group declined on cognitive function.<sup>65</sup>

293 Limitations of this study include unequal representation of age and education in the  
294 groups despite randomization, and while statistical controls were employed and age- and  
295 education-matched post hoc analyses were conducted, future research could prospectively match  
296 on these variables. Also, participants had a relatively high level of education and ethnic

297 variability was limited; additional research is needed to test generalizability. Non-completers  
298 performed worse on some cognitive and physiological measures, thus screening for minimum  
299 levels of function may be advisable.

300         Several strengths of this study are noteworthy. This study addresses a gap in the literature  
301 as no prior randomized controlled trial has compared cognitive benefits for older adults of virtual  
302 reality-enhanced exercise with traditional exercise. The observed effect exceeds that typically  
303 reported in traditional exercise research. The intervention should be applicable to a wide range of  
304 independent living older adults given the ease of using a recumbent bike and increasing  
305 availability of exergaming technologies. The finding that cognitive outcomes could be improved  
306 with cybercycling over and above traditional exercising is surprising in light of similar exercise  
307 effort, but this also provides an intriguing issue for future research to explore.

308         Follow-up studies could aim to replicate prior research by using neuroimaging to  
309 examine the impact of exergaming on brain volume in key regions (e.g., anterior cingulate cortex  
310 and hippocampus), for further evidence of neuroplasticity.<sup>13-16</sup> With a refined experimental  
311 design, future research could clarify if cognitive exercise alone is sufficient to produce the  
312 observed cognitive change, or if exergaming leads to added benefit by compounding or  
313 synergistic neurophysiological advantages when mental challenges are linked to physiological  
314 movements. Another interesting follow-up study would compare outdoor street-cycling with  
315 cybercycling, since the natural world, street obstacles, other cyclists, and way-finding would also  
316 create cognitive challenge. Safety and seasonal factors would pose challenges, but it would be  
317 interesting to evaluate biophilia factors, degree of cognitive stimulation, and social presence.  
318 Additionally, more could be done to control related factors on a cybercycle; some labs have full-  
319 surround audio-visual virtual reality environments, that could allow controlled testing of



320 “outdoor” factors while yet ensuring safety,<sup>66</sup> Last, a cost-benefit analysis of this type of  
321 intervention needs to be explored and evaluated in light of reports that physical activity  
322 interventions for inactive older adults can be cost-effective.<sup>67</sup>

323 In summary, the results of this cluster randomized clinical trial indicate that for older  
324 adults, virtual reality-enhanced interactive exercise or “cybercycling” two to three times per  
325 week for three months, yielded greater cognitive benefit and perhaps added protection from  
326 progression to MCI, than a similar dose of traditional exercise. Additional research is needed to  
327 examine the cause of this curious finding, which may be due to the presence of unique mental  
328 stimulation in virtual reality, or due to the interactive combination of cognitive and physical  
329 challenges wielding dual impacts, perhaps promoting neuroplasticity via multiple pathways.<sup>54-55</sup>  
330 The implication is that older adults who choose exergaming with interactive physical and  
331 cognitive exercise, over traditional exercise, may garner added cognitive benefit and perhaps  
332 prevent decline, all for the same exercise effort.

333

334 **Acknowledgements**

335 **Author Contributions:** Dr. Anderson-Hanley had full access to all of the data in the study and  
 336 takes responsibility for the integrity of the data and the accuracy of the data analysis.

337 *Study concept and design:* Anderson-Hanley, Arciero

338 *Acquisition of data:* Anderson-Hanley, Arciero, Nimon, Okuma

339 *Analysis and interpretation of the data:* Anderson-Hanley, Arciero, Brickman, Merz, Pence,  
 340 Westen, Woods

341 *Drafting of the manuscript:* Anderson-Hanley, Arciero

342 *Critical revision of the manuscript for important intellectual content:* Anderson-Hanley, Arciero,  
 343 Brickman, Nimon, Okuma, Zimmerman, Pence, Woods, Kramer

344 *Statistical analysis:* Anderson-Hanley, Arciero

345 *Obtained funding:* Anderson-Hanley, Arciero

346 *Administrative, technical, or material support:* Anderson-Hanley, Arciero, Nimon, Okuma

347 *Study supervision:* Anderson-Hanley, Arciero

348 **Financial Disclosures:** The authors declare no conflicts of interest.

349 **Funding/Support:** This study was funded by a grant from the Pioneer Portfolio of the Robert  
 350 Wood Johnson Foundation, through the Health Games Research national program (#64449); and  
 351 by faculty and student grants from Union and Skidmore Colleges.

352 **Role of the sponsor:** The Robert Wood Johnson Foundation had no role in the design and  
 353 conduct of the study; analysis and interpretation of the data; or preparation or approval of the  
 354 manuscript.

355 **Acknowledgement of technical support:** We acknowledge important technical assistance from:  
 356 Brian Button of Interactive Fitness Holdings regarding our use of the Espresso platform; Bruce  
 357 Winkler and Ivjot Kholi from RA Sports, LLC regarding our use of their NetAthalon cycling  
 358 software and sensor kits; Mark Martens regarding our pilot of the FitClub riding software from  
 359 Pantometrics.; John Cowan of Neurosciences Advanced Imaging Research Center, Albany  
 360 Medical Center.

361 **Acknowledgement of study sites:** We greatly appreciate the participation of the residents and  
 362 essential facilitation of the site administrators from: Beltrone Living Center, Glen Eddy,  
 363 Hightpointe Apartments, Kingsway Village, Prestwick Chase, Schaffer Heights, Wesley Health  
 364 Care (Embury Apartments and Woodlawn Commons), and Westview Apartments.

365 **Acknowledgement of research assistants:** This research could not have been possible without  
 366 the dedication of many research assistants; in particular, we would like to acknowledge: Lyndsay  
 367 De Matteo, Elliot Harmon, Veronica Hopkins, Eric Hultquist, Dinesh Kommareddy, Darlene  
 368 Landry, Shi Feng Lin, Mariale Renna, Tracey Rocha, Nick Steward, Amanda Snyder, and Vadim  
 369 Yerokhin.

370 **Acknowledgement of other contributors:** We are grateful for the thoughtful critiques and  
 371 helpful comments of those who reviewed the manuscript: Christina Brueggeman, MD, Jeffrey  
 372 Cummings, MD, Lissy Jarvik, MD, Andrew Leuchter, MD, Loretta Malta, PhD, Timothy  
 373 Nicholson, MD, and Molly Shuland, MD, as well as several anonymous reviewers.

374 **Presentation of preliminary data at professional meetings:** Earlier versions of this data were  
 375 presented at the annual meetings of the American College of Sports Medicine, the American  
 376 Psychological Association, and the Society of Behavioral Medicine.

377

378 **References**

- 379 1. Plassman BL, et al. Prevalence of dementia in the United States: The Aging,  
380 Demographics, and Memory Study. *Neuroepidemiology*. 2007;29:125-132.
- 381 2. Larson E. Prospects for delaying the rising tide of worldwide, late-life dementias. *Int*  
382 *Psychogeriatr*. 2010;22(8):1196-1202.
- 383 3. Morrison-Bogorad M, Cahan V, Wagster M. Brain health interventions: The need for  
384 further research. *Alzheimers Dem*. 2007;3:S80-S85.
- 385 4. Larson E. Physical activity for older adults at risk for Alzheimer disease. *JAMA*.  
386 2008;300(9):1077-1079.
- 387 5. Chang M, Jonsson P, Launer L, et al. The effect of midlife physical activity on cognitive  
388 function among older adults: AGES--Reykjavik Study. *J Gerontol (A Bio Sci Med Sci)*.  
389 2010;65(12):1369-1374.
- 390 6. Scarmeas N, Luchsinger J, Stern Y, et al. Physical activity, diet, and risk of Alzheimer  
391 disease. *JAMA*. 2009;302(6):627-637.
- 392 7. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and  
393 enhanced fitness to improve cognitive function in older people without known cognitive  
394 impairment. *Cochrane Database Syst Rev*. 2008;ISSN: 1469-1493X.
- 395 8. Colcombe S, Kramer, AF. Fitness effects on the cognitive function of older adults: A  
396 meta-analytic study. *Psychol Sci*. 2003;14:125-130.
- 397 9. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons  
398 with cognitive impairment and dementia: A meta-analysis. *Arch Phys Med Rehab*  
399 2004;85:1694-1704.
- 400 10. Baker LD, et al. Effects of aerobic exercise on mild cognitive impairment: A controlled  
401 trial. *Arch Neurol*. 2010;67:71-9.
- 402 11. Geda YE, et al. Physical exercise, aging, and mild cognitive impairment. *Arch Neurol*.  
403 2010;67:80-86.
- 404 12. Lautenschlager N, Cox K, Almeida O, et al. Effect of physical activity on cognitive  
405 function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA*. 2008;  
406 300:1027-1037.
- 407 13. Colcombe S, et al. Aerobic Exercise Training Increases Brain Volume in Aging Humans. *J*  
408 *Gerontol (A Bio Sci Med Sci)*. 2006;61:1166-1170.
- 409 14. Erickson K, et al. Exercise training increases size of hippocampus and improves memory  
410 *Proc Natl Acad Sci*. 2011;108(7):3017-3022.
- 411 15. Kramer A, Erickson K. Capitalizing on cortical plasticity: Influence of physical activity on  
412 cognition and brain function. *TRENDS Cog Sci*. 2007;11:342-348.
- 413 16. Pajonk FG, et al. Hippocampal plasticity in response to exercise in schizophrenia. *Arch*  
414 *Gen Psychiatry*. 2010;67:133-143.
- 415 17. Voss MW, et al. Functional connectivity: A source of variance in the association between  
416 cardiorespiratory fitness and cognition? *Neuropsychologia*. 2010;48:1394-1406.
- 417 18. Liang K, Mintun M, Head D, et al. Exercise and Alzheimer's disease biomarkers in  
418 cognitively normal older adults. *Ann Neurol* . September 2010;68(3):311-318.
- 419 19. Yaffe K. Biomarkers of Alzheimer's disease and exercise: One step closer to prevention.  
420 *Ann Neurol*.2010;68(3):275-276.
- 421 20. Knaepen K, Goekint M, Heyman E, Meeusen R. Neuroplasticity - exercise-induced  
422 response of peripheral brain-derived neurotrophic factor: a systematic review of

- 423 experimental studies in human subjects. *Sports Med (Auckland, N.Z.)*. 2010;40(9):765-  
 424 801.
- 425 21. Etnier JL, Chang YK. The effect of physical activity on executive function: a brief  
 426 commentary on definitions, measurement issues, and the current state of the literature. *J*  
 427 *Sport Exerc Psychol*. 2009;31(4):469-83.
- 428 22. Hillman C, Erickson K, Kramer A. Be smart, exercise your heart: Exercise effects on brain  
 429 and cognition. *Nat Rev Neurosci*. 2008;9(1):58-65.
- 430 23. Chodzko-Zajko W, Proctor D, Skinner J, et al. American College of Sports Medicine  
 431 position stand. Exercise and physical activity for older adults. *Medicine Sci Sports*  
 432 *Exercise*. 2009;41(7):1510-1530.
- 433 24. Reed, BD, Jensen, JD, Gorenflo, DW. Physicians and exercise promotion. *Am J Prev Med*.  
 434 1991;7(6), 410-415.
- 435 25. Grandes G, Sanchez A, Sanchez-Pinilla RO, Torcal J, Montoya I, Lizarraga K, Serra J,  
 436 PEPAF Group. Effectiveness of physical activity advice and prescription by physicians in  
 437 routine primary care: a cluster randomized trial. *Arch Intern Med*. 2009;169, 694-701.
- 438 26. Sallis J. New Thinking on Older Adults' Physical Activity. *Am J Prev Med*.  
 439 2003;25(3,Suppl2):110-111.
- 440 27. Read, JL, Shortell, SM. Interactive games to promote behavior change in prevention and  
 441 treatment. *JAMA*. 2011; published online March 29, 2011.
- 442 28. Lieberman DA. Designing serious games for learning and health in informal and formal  
 443 settings. In: *Serious games: Mechanisms and effects*, Ritterfeld U, Cody M, Vorderer P,  
 444 eds. NY: Routledge; 2009:117-130.
- 445 29. Annesi JJ, Mazas J. Effects of virtual reality-enhanced exercise equipment on adherence  
 446 and exercise-induced feeling states. *Percept Mot Skills*. 1997;85:835-44.
- 447 30. Lange BS, et al. The potential of virtual reality and gaming to assist successful aging with  
 448 disability. *Phys Med Rehabil Clin N Am*. 2010;21:339-356.
- 449 31. Chuang TY, Sung WH, Chang HA, Wang RY. Effect of a Virtual Reality–Enhanced  
 450 Exercise Protocol After Coronary Artery Bypass Grafting. *Phys Ther*. 2006;86(10):1369-  
 451 137.
- 452 32. van Schaik P, Blake J, Pernet, F, Spears I, Fencott C. Virtual augmented exercise gaming  
 453 for older adults. *CyberPsychol Behav*. 2008;11:103-106.
- 454 33. Baranowski T, Buday R, Thompson D, Baranowski J. Playing for real: Video games and  
 455 stories for health-related behavior change. *Am J Prev Med*. 2008;34(1):74-82.
- 456 34. Grealy MA, Johnson DA, Rushton SK. Improving cognitive function after brain injury: the  
 457 use of exercise and virtual reality. *Arch Phys Med Rehabil*. 1999;80:661-667.
- 458 35. Plante T, et al. Does virtual reality enhance the psychological benefits of exercise? *J*  
 459 *Human Movement Studies*. 2003;45:485-507.
- 460 36. RAND. Exercise Programs for Older Adults: A Systematic Review and Meta-analysis. CA:  
 461 Southern California Evidence-Based Practice Center. 2003.
- 462 37. Smeeth L, Ng E. Intraclass correlation coefficients for cluster randomized trials in primary  
 463 care: data from the MRC Trial of the Assessment and Management of Older People in the  
 464 Community. *Control Clin Trials*. August 2002;23(4):409-421.
- 465 38. Yang L, Reed M, Russo F, Wilkinson A. A new look at retest learning in older adults:  
 466 Learning in the absence of item-specific effects. *J Gerontol (B Psychol Sci Soc Sci)*.  
 467 2009;64B(4):470-473.

- 468 39. D'Elia LG, Satz P, Uchiyama CL, White T. Color Trails Test. Odessa, FL: Psychological  
469 Assessment Resources; 1996.
- 470 40. van der Elst W, van Boxtel MPJ, van Breukelen GJP, Jolles J. The Stroop Color-Word  
471 Test: Influence of Age, Sex, and Education; and Normative Data for a Large Sample  
472 Across the Adult Age Range. *Assessment*. 2006;13:62-79.
- 473 41. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests, 3<sup>rd</sup> Ed.  
474 NY: Oxford University Press; 2006.
- 475 42. Foster V, Hume G, Byrnes W, Dickinson A, Chatfield S. Endurance training for elderly  
476 women: moderate vs low intensity. *J Gerontol*. 1989;44(6):M184-M188.
- 477 43. Petersen R, Morris J. Mild Cognitive Impairment as a Clinical Entity and Treatment  
478 Target. *Arch Neurol*. 2005;62(7):1160-1163.
- 479 44. Jak A, Bondi M, Delis D, et al. Quantification of five neuropsychological approaches to  
480 defining mild cognitive impairment. *Amer J Geriatric Psychiatry*. 2009;17(5):368-375.
- 481 45. Saxton J, et al. (2009). Functional and cognitive criteria produce different rates of mild  
482 cognitive impairment and conversion to dementia. *J Neurol Neurosurg Psychiatry*, 80(7),  
483 737-743.
- 484 46. Kohl H, Blair S, Paffenbarger R, Macera C, Kronenfeld J. A mail survey of physical  
485 activity habits as related to measured physical fitness. *Am J Epidemiol*. 1988;127:1228-  
486 1239.
- 487 47. Etnier JL, Nowell PM, Landers DM, Sibley BA. A meta-regression to examine the  
488 relationship between aerobic fitness and cognitive performance. *Brain Res Rev*.  
489 2006;52:119-130.
- 490 48. Smiley-Oyen AL, Lowry KA, Francois SJ, Kohut ML, Ekkekakis P. Exercise, fitness, and  
491 neurocognitive function in older adults: The "selective improvement" and "cardiovascular  
492 fitness" hypotheses. *Ann Behav Med*. 2008;36:280-291.
- 493 49. Owen A, Hampshire A, Ballard C, et al. Putting brain training to the test. *Nature*.  
494 2010;465(7299):775-778.
- 495 50. Studenski S, et al. From bedside to bench: Does mental and physical activity promote  
496 cognitive vitality in late life? *Sci Aging Knowledge Environ*. 2006;10:pe21.
- 497 51. Unverzagt F, Smith D, Tennstedt S, et al. The Indiana Alzheimer Disease Center's  
498 Symposium on Mild Cognitive Impairment. Cognitive training in older adults: lessons from  
499 the ACTIVE Study. *Current Alzheimer Res*. 2009;6(4):375-383.
- 500 52. Valenzuela M, Sachdev P. Can Cognitive Exercise Prevent the Onset of Dementia?  
501 Systematic Review of Randomized Clinical Trials with Longitudinal Follow-up. *Am J*  
502 *Geriatr Psychiatry*. 2009;17:179-87.
- 503 53. Papp K, Walsh S, Snyder P. Immediate and delayed effects of cognitive interventions in  
504 healthy elderly: A review of current literature and future directions. *Alzheimer's Dementia*.  
505 2009;5(1):50-60.
- 506 54. van Praag H. Neurogenesis and exercise: Past and future directions. *Neuromolecular Med*.  
507 2008;10:128-40.
- 508 55. Fabel K, et al. Additive effects of physical exercise and environmental enrichment on adult  
509 hippocampal neurogenesis in mice. *Front Neurosci*. 2009;3:50.
- 510 56. Olson AK, Eadie BD, Ernst C, Christie, BR. Environmental enrichment and voluntary  
511 exercise massively increase neurogenesis in the adult hippocampus via dissociable  
512 pathways. *Hippocampus*. 2006;16:250-260.

- 513 57. Fabre C, Chamari K, Mucci P, Massé-Biron J, Préfaut C. Improvement of cognitive  
514 function by mental and/or individualized aerobic training in healthy elderly subjects. *Int J*  
515 *Sports Med.* 2002;23:415-421.
- 516 58. Oswald W, Gunzelmann T, Rupprecht R, Hagen B. Differential effects of single versus  
517 combined cognitive and physical training with older adults: The SimA study in a 5-year  
518 perspective. *Euro J Ageing.* 2006;3:179-192.
- 519 59. Taylor-Piliae R, Newell K, Cherin R, Lee M, King A, Haskell W. Effects of Tai Chi and  
520 Western exercise on physical and cognitive functioning in healthy community-dwelling  
521 older adults. *J Aging Phys Act.* 2010;18(3):261-279.
- 522 60. Hogan M. Physical and cognitive activity and exercise for older adults: A review. *Int J*  
523 *Aging Hum Dev.* 2005;60(2):95-126.
- 524 61. Verghese J. Cognitive and mobility profile of older social dancers. *J Am Geriatr Soc.*  
525 2006;54(8):1241-1244.
- 526 62. Nation D, Hong S, Dimsdale J, et al. Stress, exercise, and Alzheimer's disease: A  
527 neurovascular pathway. *Med Hypotheses.* 2011;76(6):847-854.
- 528 63. Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon S. Is serum brain-  
529 derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia?. *Bio*  
530 *Psychiatry.* 2009;66(6):549-553.
- 531 64. Booth FW, Lees SJ. Physically active subjects should be the control group. *Med Sci Sport*  
532 *Exerc.* 2006;38:405–406.
- 533 65. Hill R, Storandt M, Malley M. The impact of long-term exercise training on psychological  
534 function in older adults. *J Gerontol.* 1993;48(1):P12-P17.
- 535 66. Kwon, D.S. et al. KAIST interactive bicycle racing simulator: The 2nd version with  
536 advanced features. *Intelligent Robots and System 2002 IEEEERSJ International Conference.*  
537 2002; 3, 2961-2966.
- 538 67. Sevick M, Dunn A, Morrow M, Marcus B, Chen G, Blair S. Cost-effectiveness of lifestyle  
539 and structured exercise interventions in sedentary adults: results of project ACTIVE. *Am J*  
540 *Prev Med.* 2000;19(1):1-8.
- 541

542

543 **List of Tables & Figures:**

544 **TABLE 1.** Baseline Characteristics of Trial Participants.

545 **TABLE 2.** Neuropsychological and Physiological Outcomes After Three Months of Exercise

546 (Intent-to-Treat Analysis).

547 **TABLE 3.** Exercise Behavior Outcomes After Three Months of Exercise: Cybercycle vs.

548 Control Bike.

549 **FIGURE 1.** CONSORT diagram showing flow of participants from screening to post-exercise

550 evaluation.

551 **FIGURE 2.** Change in executive function composite before and after three months of exercise.

552 Note: Cybercyclists represented by solid line; control cyclists represented by the dashed line;

553  $n=79$ ; mixed linear model (random effects: age, education, and cluster) group x time interaction

554 significant ( $p=.002$ ).

**TABLE 1.** Baseline Characteristics of Trial Participants

	cybercycle (n = 38)		control bike (n = 41)	
Age, mean (SD), y <sup>1</sup>	75.7	(9.9)	81.6	(6.2)
Women, No. (%)	33	(70.7)	29	(86.8)
Education, mean (SD), y <sup>1</sup>	12.6	(2.2)	14.8	(2.3)
Physiological Factors, mean (SD)				
Weight, kg	75.0	(13.1)	72.1	(15.9)
BMI	29.0	(4.7)	27.4	(6.3)
Fat Mass, kg	31.8	(8.0)	28.0	(11.7)
Lean Mass, kg	40.6	(6.3)	41.9	(6.8)
Abdominal Fat, %	47.4	(8.4)	39.9	(12.4)
Insulin, uU/mL	10.7	(5.0)	9.9	(8.0)
Glucose, mM/L	6.4	(2.0)	5.5	(0.6)
Physical activity level, daily kcal <sup>2</sup>	301.3	(218.0)	307.2	(215.3)
Neuropsychological Measures, mean (SD)				
Intelligence Proxy (NAART), IQ	117.6	(8.7)	120.6	(5.2)
Executive Function				
Color Trails Difference (2-1), s	55.2	(30.7)	75.6	(64.8)
Stroop C, s	67.3	(35.7)	68.7	(35.8)
Digits Backwards, sum score	5.8	(1.9)	6.5	(2.1)
Attention				
LDST, sum score	29.2	(7.1)	29.1	(6.6)
Verbal Fluency				
COWAT, sum score	33.1	(15.5)	37.8	(12.4)
Categories, sum score	15.9	(4.2)	16.1	(4.6)
Verbal Memory (immediate)				
RAVLT, sum 5 trials score	36.1	(12.1)	38.9	(9.5)
RAVLT Immediate Recall, score	7.2	(2.9)	7.2	(3.8)
Verbal Memory (delayed)				
RAVLT Delayed Recall, score	6.9	(3.6)	6.8	(3.9)
Fuld Delayed Recall, score	7.6	(2.7)	7.2	(1.8)
Visuospatial Skill				
Figure Copy, sum score	26.3	(5.8)	27.1	(7.2)
Clock, sum score	5.8	(1.4)	6.1	(1.3)
Visuospatial Memory (delayed)				
Figure Delayed Recall, score	8.8	(6.2)	9.6	(4.7)
Motor Function				
Pegboard Dominant Hand, s	120.7	(50.1)	130.0	(44.6)
Pegboard NonDom Hand, s	136.1	(85.7)	139.3	(47.1)
Clinical Status, No. (%)				
MCI ( $\geq 1$ domain: $\leq -1.5$ SD of norm)	16	(42.1)	14	(34.1)

Abbreviations: BMI, Body Mass Index; NAART, North American Adult Reading Test; LDST, Letter Digit Symbol Test; COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test.

<sup>1</sup> Group difference at baseline on age ( $p = .002$ ) and education ( $p < .001$ ).

<sup>2</sup> Physical activity level (daily kcal) was estimated in Year 1 via questionnaire and Year 2 via Actical (see Methods).



**TABLE 2.** Neuropsychological and Physiological Outcomes After Three Months of Exercise (Intent-to-Treat Analysis)<sup>a</sup>

	Mean Difference From Baseline (95% CI)		$p$ (Degrees of Freedom) ANCOVA
	Cybercycle (n = 38)	Control Bike (n = 41)	Repeated Measures Group x Time <sup>b</sup>
Primary Cognitive Outcomes:			
Executive Function			
Color Trails Difference (2-1), s	-15.94 (-16.21 to -15.66)	9.74 (9.48 to 10.00)	.007 (1, 73)
Stroop C, s	-6.59 (-6.67 to -6.51)	0.56 (0.49 to 0.64)	.05 (1, 73)
Digits Backwards, sum score	0.36 (0.34 to 0.38)	-0.83 (-0.85 to -0.82)	.03 (1, 73)
Secondary Cognitive Outcomes <sup>c</sup> :			
Attention			
LDST, sum score	0.79 (0.62 to 0.95)	0.73 (0.57 to 0.89)	.95 (1, 72)
Verbal Fluency			
COWAT, sum score	3.51 (2.77 to 4.25)	2.33 (1.62 to 3.03)	.63 (1, 73)
Categories, sum score	-0.03 (0.11 to -0.18)	1.18 (1.32 to 1.04)	.22 (1, 73)
Verbal Memory (immediate)			
RAVLT, sum 5 trials score	-0.73 (-1.27 to -0.19)	0.85 (0.33 to 1.37)	.50 (1, 73)
RAVLT Immediate Recall, score	0.77 (0.60 to 0.94)	0.06 (-0.10 to 0.22)	.32 (1, 73)
Verbal Memory (delayed)			
RAVLT Delayed Recall, score	0.71 (0.62 to 0.79)	0.10 (0.01 to 0.18)	.43 (1, 73)
Fuld Delayed Recall, score	0.15 (0.13 to 0.17)	0.39 (0.37 to 0.41)	.61 (1, 73)
Visuospatial Skill			
Figure Copy, sum score	3.27 (3.56 to 2.98)	3.69 (3.97 to 3.40)	.81 (1, 72)
Clock, sum score	0.07 (0.07 to 0.07)	-0.19 (-0.19 to -0.19)	.45 (1, 72)
Visuospatial Memory (delayed)			
Figure Delayed Recall, score	0.07 (0.22 to -0.08)	1.66 (1.80 to 1.52)	.28 (1, 72)
Motor Function			
Pegboard Dominant Hand, s	10.61 (8.64 to 12.57)	6.13 (4.22 to 8.03)	.56 (1, 72)
Pegboard NonDom Hand, s	7.76 (5.86 to 9.65)	13.79 (11.95 to 15.63)	.36 (1, 72)
Physiological Outcomes:			
Weight, kg	-0.63 (-0.75 to -0.52)	-0.04 (-0.15 to 0.07)	.24 (1, 72)
Body Mass Index	-0.26 (-0.29 to -0.23)	-0.03 (-0.06 to 0.00)	.26 (1, 67)
Fat Mass, kg	-1.04 (-0.95 to -1.13)	-0.76 (-0.67 to -0.84)	.50 (1, 72)
Lean Mass, kg	0.39 (0.31 to 0.47)	0.56 (0.48 to 0.63)	.65 (1, 72)
Abdominal Fat, %	-1.79 (-1.97 to -1.61)	-0.94 (-1.11 to -0.78)	.32 (1, 66)
Leg Extension 60°, s <sup>-1</sup>	-2.96 (-3.00 to -2.92)	11.09 (11.05 to 11.13)	.04 (1, 71)
Leg Flex 60°, s <sup>-1</sup>	-2.79 (-3.26 to -2.31)	5.70 (5.25 to 6.15)	.07 (1, 71)
Insulin, uU/mL	2.75 (2.39 to 3.12)	1.53 (1.16 to 1.90)	.46 (1, 67)
Glucose, mM/L	-0.09 (-0.01 to -0.16)	-0.06 (0.01 to -0.13)	.90 (1, 68)

Abbreviations: LDST, Letter Digit Symbol Test; COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test.

<sup>a</sup> Marginal mean differences and CIs reported based on repeated measures ANCOVA controlling for age and education.

<sup>b</sup> The first degree of freedom in parentheses refers to the effect (group x time) and the second refers to the error term.

<sup>c</sup> No significant changes expected given prior research literature.

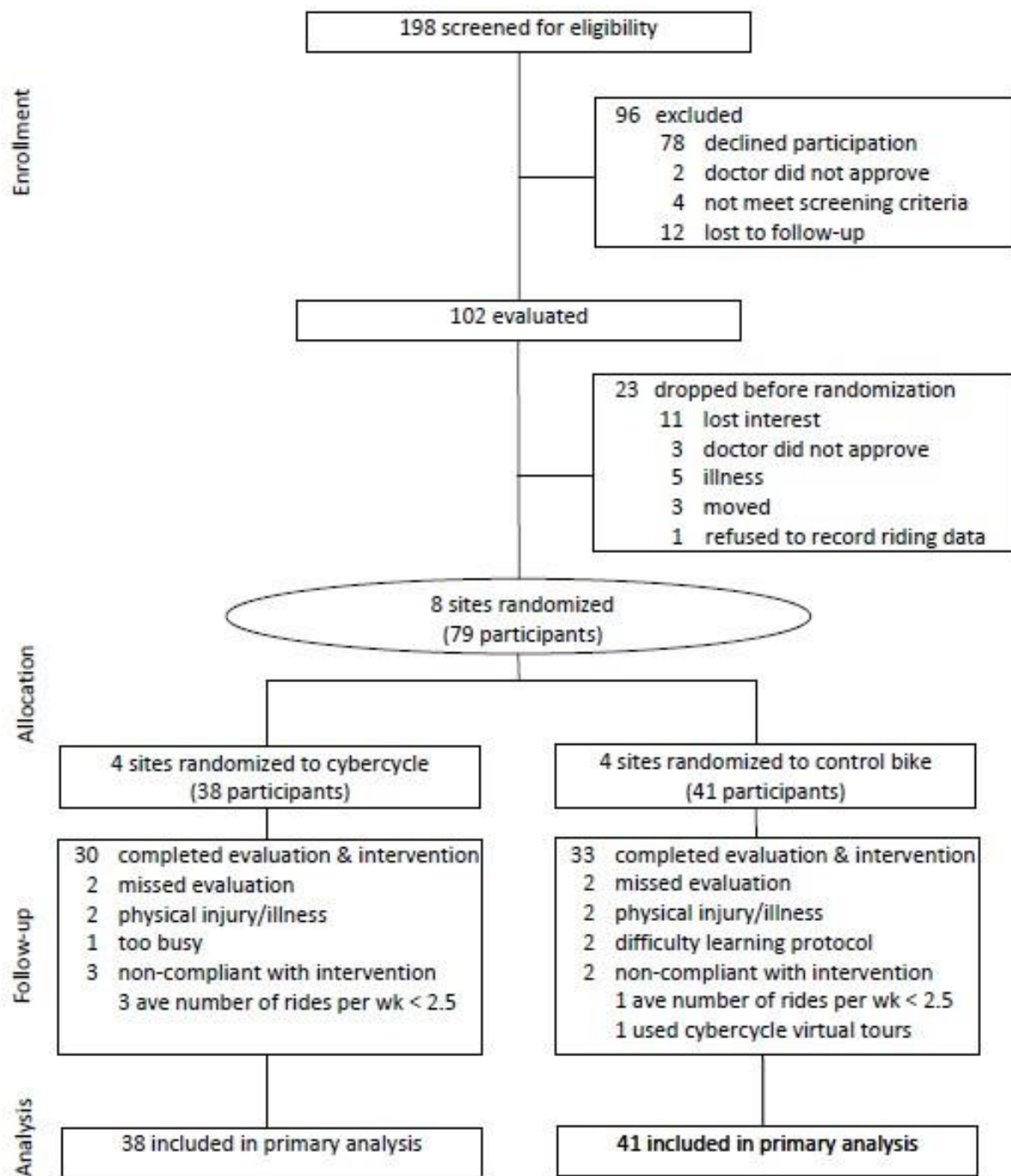
**TABLE 3.** Exercise Behavior Outcomes After Three Months of Exercise: Cybercycle vs. Control Bike<sup>a</sup>

	Mean (SD)		Difference Between Interventions Mean, (95% CI)	P Value (Degrees of Freedom)
	Cybercycle (n = 30)	Control Bike (n = 33)		
Exercise Behavior Outcomes:				
Frequency of Rides, n	51.3 (3.32)	53.3 (3.14)	-1.96 (-2.31 to -1.61)	.68 (1, 59)
Power, watts <sup>b</sup>	36.3 (3.28)	32.1 (3.15)	4.20 (3.93 to 4.46)	.44 (1, 31)
Energy Expended, kcal	107.9 (8.05)	93.6 (7.63)	14.32 (13.47 to 15.17)	.23 (1, 59)
Duration, m	35.5 (1.81)	33.8 (1.72)	1.61 (1.42 to 1.80)	.54 (1, 59)
Distance Average, miles	5.4 (0.40)	4.8 (0.38)	0.65 (0.61 to 0.69)	.27 (1, 59)
Distance Total, miles	283.9 (28.80)	261.4 (27.29)	22.51 (19.47 to 25.54)	.59 (1, 59)
Speed Average, mph <sup>b</sup>	7.4 (0.38)	8.3 (0.37)	-0.83 (-0.86 to -0.80)	.19 (1, 31)
Speed Peak, mph <sup>b</sup>	10.7 (0.39)	9.8 (0.37)	0.97 (0.94 to 1.00)	.13 (1, 31)
Physical Activity Daily, kcal	324.4 (32.91)	304.2 (32.22)	20.22 (0.94 to 1.00)	.66 (1, 43)

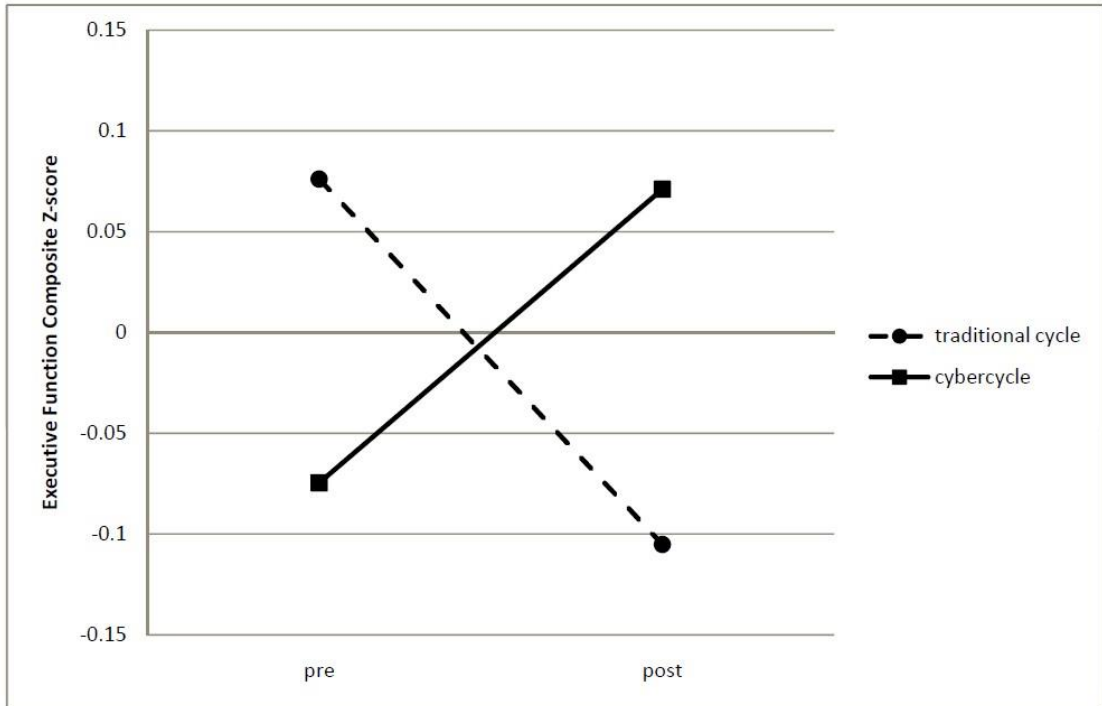
<sup>a</sup> Marginal means and SDs reported based on ANCOVA controlling for age and education.

<sup>b</sup> Samples sizes: cybercycle (n = 17) and control bike (n = 18) due to enhanced ride data available in Year 2.

Figure



Figure



**Content of the Supplemental Online Materials**

Figure 1 – Cybercycle Demonstration and Screen Shot

Table 1 – Neuropsychological and Physiological Outcomes: Age-Matched

Table 2 - Exercise Behavior Outcomes After Three Months of Exercise: Age-Matched

Table 3 – Characteristics of Completers vs. Non-Completers

Table 4 – Neuropsychological and Physiological Outcomes: Complete-Case Analysis

Table 5 – Adverse Events

Figure 1 - Neuropsychological and Physiological Outcomes: Three Executive Function Measures and BDNF

TextFile 1 – Exercise Equipment Specifications

TextFile 2 – Details of Cognitive Measures

TextFile 3 – Details of ELISA Analyses

FIGURE 1. Cybercycle demonstration image and screen shot of virtual terrain and avatars.



**TABLE 1. Neuropsychological and Physiological Outcomes: Age and Education-Matched<sup>a</sup>**

	Mean Difference From Baseline (95% CI)		P (Degrees of Freedom) ANCOVA
	Cybercycle (n = 26)	Control Bike (n = 26)	Repeated Measures Group x Time <sup>b</sup>
<b>Primary Cognitive Outcomes:</b>			
<b>Executive Function</b>			
Color Trails Difference (2-1), s	-15.67 (-28.22 to -3.12)	14.08 (0.93 to 27.23)	.008 (1, 46)
Stroop C, s	-6.57 (-15.01 to 1.88)	0.96 (-7.53 to 9.45)	.05 (1, 46)
Digits Backwards, sum score	0.23 (-0.53 to 0.99)	-1.38 (-2.14 to -0.63)	.01 (1, 47)
<b>Secondary Cognitive Outcomes<sup>c</sup>:</b>			
<b>Attention</b>			
LDST, sum score	1.22 (-1.11 to 3.56)	0.90 (-1.55 to 3.35)	.77 (1, 46)
<b>Verbal Fluency</b>			
COWAT, sum score	3.82 (-1.18 to 8.81)	2.10 (-2.97 to 7.17)	.57 (1, 47)
Categories, sum score	0.66 (-0.90 to 2.22)	1.26 (-0.33 to 2.85)	.61 (1, 47)
<b>Verbal Memory (immediate)</b>			
RAVLT, sum 5 trials score	-0.61 (-3.92 to 2.70)	0.01 (-3.32 to 3.33)	.82 (1, 46)
RAVLT Immediate Recall, score	0.97 (-0.18 to 2.11)	-0.17 (-1.29 to 0.95)	.22 (1, 45)
<b>Verbal Memory (delayed)</b>			
RAVLT Delayed Recall, score	0.60 (-0.71 to 1.92)	-0.14 (-1.43 to 1.15)	.46 (1, 45)
Fuld Delayed Recall, score	0.14 (-0.58 to 0.86)	0.32 (-0.40 to 1.05)	.73 (1, 48)
<b>Visuospatial Skill</b>			
Figure Copy, sum score	4.16 (1.96 to 6.36)	4.70 (2.40 to 6.99)	.79 (1, 46)
Clock, sum score	-0.18 (-0.59 to 0.23)	-0.29 (-0.71 to 0.13)	.06 (1, 48)
<b>Visuospatial Memory (delayed)</b>			
Figure Delayed Recall, score	0.46 (-1.58 to 2.49)	2.90 (0.72 to 5.08)	.11 (1, 45)
<b>Motor Function</b>			
Pegboard Dominant Hand, s	11.35 (-4.98 to 27.68)	8.30 (-8.46 to 25.07)	.69 (1, 47)
Pegboard NonDom Hand, s	7.38 (-9.88 to 24.64)	13.31 (-3.88 to 30.50)	.43 (1, 46)
<b>Physiological Outcomes:</b>			
Weight, kg	-0.70 (-7.02 to 5.62)	0.03 (-6.29 to 6.35)	.16 (1, 48)
Body Mass Index	-0.26 (-2.60 to 2.09)	-0.01 (-2.35 to 2.34)	.20 (1, 48)
Fat Mass, kg	-1.15 (-5.54 to 3.24)	-0.92 (-5.32 to 3.49)	.61 (1, 48)
Lean Mass, kg	0.43 (-2.36 to 3.22)	0.73 (-2.06 to 3.52)	.41 (1, 48)
Abdominal Fat, %	-1.86 (-6.36 to 2.64)	-0.93 (-5.45 to 3.60)	.35 (1, 45)
Leg Extension 60°, s <sup>-1</sup>	-2.06 (-12.66 to 8.54)	14.91 (3.98 to 25.84)	.05 (1, 46)
Leg Flex 60°, s <sup>-1</sup>	-1.75 (-8.73 to 5.24)	9.23 (1.96 to 16.49)	.07 (1, 46)
Insulin, uU/mL	3.48 (0.58 to 6.38)	1.87 (-1.14 to 4.89)	.43 (1, 46)
Glucose, mM/L	0.04 (-0.29 to 0.37)	-0.14 (-0.50 to 0.21)	.24 (1, 43)

Abbreviations: LDST, Letter Digit Symbol Test; COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test.

Note: when more than one participant of the same age was available for matching, the decision was made based on matching education and/or sex.

<sup>a</sup> Marginal means and SDs reported based on repeated measures ANCOVA controlling for age and education.

<sup>b</sup> The first degree of freedom in parentheses refers to the effect (group x time) and the second refers to the error term.

<sup>c</sup> No significant changes expected given prior research literature.

<sup>d</sup> Sample sizes: cybercycle (n = 12) and control bike (n = 11) due to missing biomarker data.

**TABLE 2.** Exercise Behavior Outcomes After Three Months of Exercise: Age and Education-Matched<sup>a</sup>

	Mean (SD)		Difference Between Interventions Mean, (95% CI)	P Value (Degrees of Freedom)
	Cybercycle (n = 30)	Control Bike (n = 33)		
Exercise Behavior Outcomes:				
Frequency of Rides, n	51.3 (3.32)	53.3 (3.14)	-1.96 (-2.31 to -1.61)	.68 (1, 59)
Power, watts <sup>b</sup>	36.3 (3.28)	32.1 (3.15)	4.20 (3.93 to 4.46)	.44 (1, 31)
Energy Expended, kcal	107.9 (8.05)	93.6 (7.63)	14.32 (13.47 to 15.17)	.23 (1, 59)
Duration, m	35.5 (1.81)	33.8 (1.72)	1.61 (1.42 to 1.80)	.54 (1, 59)
Distance Average, miles	5.4 (0.40)	4.8 (0.38)	0.65 (0.61 to 0.69)	.27 (1, 59)
Distance Total, miles	283.9 (28.80)	261.4 (27.29)	22.51 (19.47 to 25.54)	.59 (1, 59)
Speed Average, mph <sup>b</sup>	7.4 (0.38)	8.3 (0.37)	-0.83 (-0.86 to -0.80)	.19 (1, 31)
Speed Peak, mph <sup>b</sup>	10.7 (0.39)	9.8 (0.37)	0.97 (0.94 to 1.00)	.13 (1, 31)
Physical Activity Daily, kcal	324.4 (32.91)	304.2 (32.22)	20.22 (0.94 to 1.00)	.66 (1, 43)

<sup>a</sup> Marginal means and SDs reported based on ANCOVA controlling for age and education.

<sup>b</sup> Samples sizes: cybercycle (n = 17) and control bike (n = 18) due to enhanced ride data available in Year 2.



**TABLE 3. Characteristics of Completers vs. Non-Completers**

	Cybercycle			Control Bike		
	Completers (n = 30)	Nn- Completers (n = 8)	<i>p</i> Value	Completers (n = 33)	Nn- Completers (n = 8)	<i>p</i> Value
Age, mean (SD), y	76.1 (10.3)	74.0 (8.3)	.62	81.6 (6.3)	81.8 (5.7)	.94
Women, No. (%)	25 (83.3)	8 (100)	.27	21 (63.6)	8 (100)	.06
Education, mean (SD), y	12.7 (2.4)	11.9 (0.9)	.35	14.8 (2.3)	14.5 (2.1)	.72
Physiological Factors, mean (SD)						
Weight, kg	74.8 (13.7)	75.9 (10.9)	.86	73.3 (17.0)	66.8 (8.7)	.33
BMI	28.6 (4.7)	31.2 (5.0)	.23	27.8 (6.6)	25.7 (4.5)	.44
Fat Mass, kg	31.4 (8.4)	33.9 (5.9)	.49	28.0 (12.4)	28.1 (8.8)	.98
Lean Mass, kg	40.9 (6.7)	39.1 (4.5)	.53	43.0 (6.9)	36.7 (2.8)	.02
Abdominal Fat, %	46.6 (8.2)	55.3 (5.4)	.09	39.5 (12.5)	41.9 (12.8)	.65
Insulin, uU/mL	11.1 (5.3)	8.8 (1.9)	.31	9.9 (8.2)	9.9 (7.9)	.99
Glucose, mM/L	6.0 (0.9)	8.6 (4.0)	.002	5.5 (0.7)	5.4 (0.6)	.68
Physical activity level, daily kcal	286.9 (234.3)	339.7 (180.3)	.63	312.8 (226.2)	288.2 (195.3)	.83
Neuropsychological Measures, mean (SD)						
Intelligence Proxy (NAART), IQ	118.9 (8.9)	112.6 (6.3)	.09	120.9 (5.0)	119.5 (6.1)	.52
Executive Function						
Color Trails Difference (2-1), s	58.4 (30.2)	84.3 (90.8)	.19	59.1 (28.2)	79.7 (47.1)	.12
Stroop C, s	58.2 (21.8)	72.0 (50.0)	.27	55.5 (17.3)	77.9 (50.0)	.04
Digits Backwards, sum score	6.2 (1.5)	5.0 (1.6)	.08	6.9 (2.2)	6.1 (1.8)	.33
Attention						
LDST, sum score	30.1 (7.2)	27.0 (7.1)	.31	30.7 (5.7)	25.5 (6.3)	.03
Verbal Fluency						
COWAT, sum score	33.0 (14.1)	32.4 (11.7)	.93	39.8 (11.8)	33.8 (12.3)	.20
Categories, sum score	12.1 (3.4)	13.0 (2.4)	.51	11.6 (4.2)	13.0 (3.4)	.38
Verbal Memory (immediate)						
RAVLT, sum 5 trials score	36.7 (9.5)	28.0 (5.7)	.03	35.8 (9.2)	35.9 (9.3)	.97
RAVLT Immediate Recall, score	6.3 (3.0)	4.0 (3.2)	.09	6.0 (2.9)	5.6 (2.2)	.71
Verbal Memory (delayed)						
RAVLT Delayed Recall, score	6.1 (3.2)	2.9 (2.9)	.02	5.6 (3.4)	6.1 (2.2)	.66
Fuld Delayed Recall, score	7.3 (1.5)	6.9 (0.7)	.43	7.0 (1.9)	6.9 (1.5)	.86
Visuospatial Skill						
Figure Copy, sum score	25.9 (4.3)	25.5 (5.3)	.82	26.8 (6.0)	24.1 (6.5)	.29
Clock, sum score	6.5 (1.1)	5.3 (2.1)	.05	6.7 (1.0)	6.0 (1.2)	.11
Visuospatial Memory (delayed)						
Figure Delayed Recall, score	12.6 (5.3)	10.1 (4.2)	.26	11.8 (5.6)	11.7 (5.2)	.96
Motor Function						
Pegboard Dominant Hand, s	109.2 (47.0)	103.3 (19.7)	.75	112.9 (32.1)	132.4 (33.3)	.14
Pegboard NonDom Hand, s	120.4 (59.8)	118.7 (26.7)	.94	126.2 (37.5)	143.1 (40.2)	.27

Abbreviations: BMI, Body Mass Index; NAART, North American Adult Reading Test; LDST, Letter Digit Symbol Test; COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test.

**TABLE 4.** Neuropsychological and Physiological Outcomes After Three Months of Exercise (Complete-Case Analysis)<sup>a</sup>

	Mean Difference From Baseline (95% CI)		<i>p</i> (Degrees of Freedom)
	Cybercycle (n = 30)	Control Bike (n = 33)	ANCOVA Repeated Measures Group x Time <sup>b</sup>
<b>Primary Cognitive Outcomes:</b>			
<b>Executive Function</b>			
Color Trails Difference (2-1), s	-17.61 (-19.70 to -15.52)	10.85 (8.79 to 12.90)	.005 (1, 57)
Stroop C, s	-6.18 (-7.37 to -4.98)	1.07 (-0.06 to 2.20)	.04 (1, 57)
Digits Backwards, sum score	0.39 (0.29 to 0.49)	-1.12 (-1.21 to -1.02)	.007 (1, 57)
<b>Secondary Cognitive Outcomes<sup>c</sup>:</b>			
<b>Attention</b>			
LDST, sum score	0.88 (0.65 to 1.11)	0.55 (0.33 to 0.77)	.78 (1, 57)
<b>Verbal Fluency</b>			
COWAT, sum score	4.04 (3.17 to 4.91)	2.37 (1.53 to 3.20)	.54 (1, 58)
Categories, sum score	0.54 (0.68 to 0.41)	1.27 (1.40 to 1.14)	.49 (1, 58)
<b>Verbal Memory (immediate)</b>			
RAVLT, sum 5 trials score	-0.41 (-1.05 to 0.22)	0.69 (0.09 to 1.29)	.68 (1, 57)
RAVLT Immediate Recall, score	0.92 (0.75 to 1.09)	-0.02 (-0.18 to 0.14)	.24 (1, 56)
<b>Verbal Memory (delayed)</b>			
RAVLT Delayed Recall, score	0.61 (0.50 to 0.72)	0.00 (-0.11 to 0.10)	.49 (1, 56)
Fuld Delayed Recall, score	0.10 (0.09 to 0.11)	0.27 (0.26 to 0.29)	.74 (1, 59)
<b>Visuospatial Skill</b>			
Figure Copy, sum score	4.00 (4.39 to 3.60)	3.95 (4.34 to 3.56)	.98 (1, 57)
Clock, sum score	-0.08 (-0.13 to -0.03)	-0.16 (-0.21 to -0.11)	.84 (1, 59)
<b>Visuospatial Memory (delayed)</b>			
Figure Delayed Recall, score	0.12 (0.38 to -0.14)	1.99 (2.25 to 1.74)	.27 (1, 56)
<b>Motor Function</b>			
Pegboard Dominant Hand, s	10.91 (9.38 to 12.43)	7.70 (6.23 to 9.17)	.67 (1, 58)
Pegboard NonDom Hand, s	8.09 (4.83 to 11.34)	14.96 (11.88 to 18.04)	.34 (1, 57)
<b>Physiological Outcomes:</b>			
Weight, kg	-0.58 (-0.72 to -0.44)	0.12 (-0.01 to 0.26)	.18 (1, 59)
Body Mass Index	-0.21 (-0.25 to -0.16)	0.03 (-0.01 to 0.07)	.24 (1, 59)
Fat Mass, kg	-1.04 (-0.92 to -1.15)	-0.77 (-0.66 to -0.88)	.56 (1, 59)
Lean Mass, kg	0.45 (0.37 to 0.52)	0.67 (0.59 to 0.74)	.56 (1, 59)
Abdominal Fat, %	-1.80 (-2.06 to -1.54)	-0.86 (-1.12 to -0.61)	.31 (1, 56)
Leg Extension 60°, s <sup>-1</sup>	-2.85 (-2.72 to -2.98)	12.15 (12.28 to 12.02)	.06 (1, 56)
Leg Flex 60°, s <sup>-1</sup>	-2.70 (-3.01 to -2.40)	6.80 (6.50 to 7.11)	.08 (1, 56)
Insulin, uU/mL	3.23 (2.75 to 3.71)	1.54 (1.08 to 2.01)	.36 (1, 56)
Glucose, mM/L	0.00 (-0.07 to 0.07)	-0.10 (-0.18 to -0.03)	.54 (1, 54)

Abbreviations: LDST, Letter Digit Symbol Test; COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Test.

<sup>a</sup> Marginal means and SDs reported based on repeated measures ANCOVA controlling for age and education.

<sup>b</sup> The first degree of freedom in parentheses refers to the effect (group x time) and the second refers to the error term.

<sup>c</sup> No significant changes expected given prior research literature.

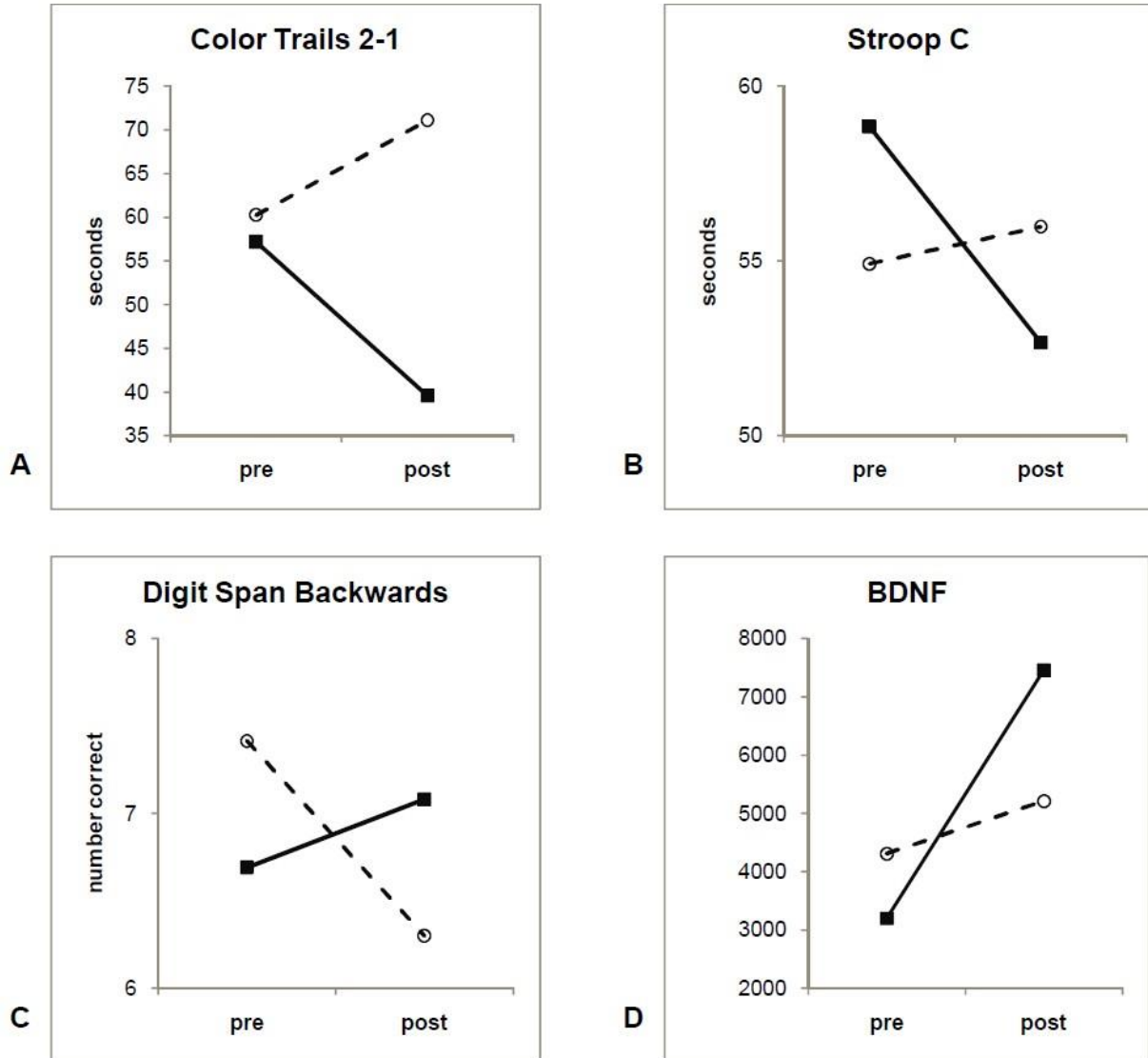
<sup>d</sup> Sample sizes: cybercycle (n = 14) and control bike (n = 17) due to missing biomarker data.

**TABLE 5.** Adverse Events and Discontinuation of Intervention During 3-Month Exercise Intervention

	Cybercycle Group	Control Bike Group
Total adverse events reported	7	6
Knee or sciatica pain while cycling	2 <sup>a</sup>	2
Acute illness (upper respiratory to ER)		1
Other injuries (hurt back lifting, car accident)	1	1
Cancer diagnosis and treatment	2	
Frustrated interacting with bike computer	1	2
Vertigo while cycling	1 <sup>a</sup>	

<sup>a</sup> These 2 events occurred in the same participant. For some riders the sense of motion evoked by virtual scenery may induce vertigo; this was rare in this study, perhaps due to the use of a recumbent bike which provides greater distance from the video display.

Figure 1. Neuropsychological and Physiological Outcomes: Three Executive Function Measures and BDNF



Note: Change in executive function and BDNF before and after three months of exercise. Cybercyclists represented by solid line; control cyclists represented by the dashed line. (A) Color Trails 2-1; (B) Stroop C; (C) Digits Span Backwards; (D) BDNF. Group x time interactions, controlling for age and education, were significant ( $p=.007, .05, .03, .05$ , respectively).

TEXT FILE 1 – Exercise Equipment Specifications

Bicycles in both years of the study were recumbent, with a “walk-through” design (affording an open space to step in between the seat and steering mechanism so that participants did not have to lift their leg over a center bar), and all bikes had gear shifts so participants could adjust the pedaling resistance. The cycles were identical across the cybercycle and traditional bicycle conditions except that the additional interactive virtual reality display that was enabled in the cybercycle condition. In Year 1, a recumbent Tunturi stationary bike (e60r) was utilized and interfaced with Netathlon riding software (v. 2.0) on an Acer laptop. Many participants were novice computer users and some had functional issues (e.g., arthritis in their hands) that made it difficult to use the computer components (e.g., learning to “mouse”). In Year 2, a different exergame setup was sought and the recumbent Espresso bike (S3R) was chosen since the computer components were more seamlessly integrated and included a touchpad that was easier to operate. In both years, participants in the cybercycle condition observed their avatar on the screen as a virtual rider traveling a virtual 3D terrain. There were no significant differences between years in ride frequency, intensity or duration.

TEXT FILE 2 – Details of Cognitive Measures

The primary cognitive domain of executive function was assessed by: Color Trails 2-1 difference score (time to connect dots alternating colors and numbers, minus time to connect numbers),<sup>1</sup> Stroop C (time to state the ink color while suppressing the contrasting typed color name),<sup>2</sup> and Digit Span Backwards (number of correct trials repeating a string of numbers in reverse order).<sup>3</sup>

Secondary cognitive domains included: 1) attention: Letter Digit Symbol Test (LDST; number of correct matches for digit-letter pairs within 60s; range 0-25)<sup>4</sup>; 2) verbal fluency: Controlled Word Association Test (COWAT; number of words within one minute that start with a given letter)<sup>3</sup>; 3) and category fluency (number of words within one minute that fit a given category)<sup>3</sup>; 4) verbal memory, immediate: Rey Auditory Verbal Learning Task (RAVLT; sum of five trials to learn a list of 15 words; range 0-75)<sup>3</sup> and RAVLT recall (number recalled of the practiced list after a distracter list)<sup>3</sup>; 5) verbal memory, delayed: RAVLT delay (recall of the practiced list after a 20 minute delay)<sup>3</sup> and Fuld Object Memory Evaluation (Fuld; number of objects from a bag recalled after a 20 minute delay; range 0-10)<sup>5</sup>; 6) visuospatial skill: Complex Figure copy (score assigned by at least two raters for copying an arrangement of geometric shapes; range 0-36)<sup>3</sup> and Clock (score assigned by at least two raters for drawing a clock with hands at a given time; range 0-8)<sup>6</sup>; 7) visuospatial memory: Complex Figure recall (scored by at least two raters for reproducing the previously copied figure after a 30 minute delay)<sup>3</sup>; and 8) motor function: Grooved Pegboard (time to fill a pegboard with pegs; first with dominant and then non-dominant hand)<sup>3</sup>.

Alternate forms of tests were used at each subsequent evaluation.

TEXT FILE 2 – Details of Cognitive Measures (continued)

References for Cognitive Measures:

1. D’Elia LG, Satz P, Uchiyama CL, White T. *Color Trails Test*. Odessa, FL: Psychological Assessment Resources; 1996.
2. van der Elst W, van Boxtel MPJ, van Breukelen GJP, Jolles J. The Stroop Color-Word Test: Influence of Age, Sex, and Education; and Normative Data for a Large Sample Across the Adult Age Range. *Assessment*. 2006;13:62-79.
3. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests, 3<sup>rd</sup> Ed.* NY: Oxford University Press; 2006.
4. van der Elst W, van Boxtel MPJ, van Breukelen GJP, Jolles J (2006) The Letter Digit Substitution Test: Normative Data for 1,858 Healthy Participants Aged 24-81 from the Maastricht Aging Study (MAAS): Influence of Age, Education, and Sex. *J Clin Exper Neuropsychol* 28:998-1009.
5. Fuld PA, Masur DM, Blau AD, Crystal H, Aronson MK. (1990) Object-memory evaluation for prospective detection of dementia in normal functioning elderly: Predictive and normative data. *J Clin Exper Neuropsychol* 12:520–528.
6. LaRue A, Romero LJ, Ortiz IE, Liang HC, Lindeman RD (1999) Neuropsychological performance of Hispanic and non-Hispanic older adults: an epidemiologic survey. *Clin Neuropsychol* 13:474-86.

TEXT FILE 3 – Details of ELISA analyses

Intra-and inter-assay coefficients of variation were 3.7 and 8.5%, respectively.

Ethylenediaminetetraacetic acid (EDTA) plasma samples were diluted 2-4X and assayed against a standard curve with a 2000 pg·ml<sup>-1</sup> highest concentration. The supplied kit reagents were used as described in the manufacturer's instructions, and the plate was read at 450 nm on a spectrophotometric plate reader (BioTek, Winooski, VT).