Exergaming Improves Older Adult Cognition: A Cluster Randomized Clinical Trial

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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 Identifier: NCT01167400

Introduction

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

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

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

Although promising, there are limited published data on whether interactive exergaming technologies are reliably associated with enhanced physical and cognitive health outcomes, and more controlled research on the effects of health games is needed.[27,33] One early study[34] investigated virtual reality-enhanced stationary cycling using virtual tours and on-screen competition, we refer to as “cybercycling,” and found cognitive improvement in patients with traumatic brain injury. However, without a traditional exercise control group, it is unclear whether cybercycling yielded cognitive benefit beyond physical exercise alone. While there are reports of the psychological benefits of cybercycling,[29,30,35] no previous randomized controlled trial has evaluated the cognitive benefits of virtual reality-enhanced exercise. Presented herein are results of the Cybercycle Study, a multi-site cluster randomized clinical trial in which the cognitive benefit of cybercycling was compared with traditional stationary cycling, for independent living older adults. Based on prior research showing primarily executive function gains from exercise, [8,21,22] it was hypothesized that cybercycling would yield greater executive function. Further, it was hypothesized that any change would be due to increased exercise effort spurred on by engaging interactive virtual tours, competition and added mental challenge. Secondary analyses examined change in BDNF as a biomarker indicating possible neuroplasticity which has been implicated as a mechanism of change linking exercise to cognition.[10,14,18-20]

Methods

Design

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

Setting and Participants

Participants were recruited by fliers and information sessions at eight independent living facilities. The facilities were chosen because of proximity to investigator institutions, similarity in size (average 100-200 residents), and presence of contiguous living areas to ensure indoor access to a study bike (to minimize barriers associated with travel). Participants volunteered based on demonstrations of cybercycle functionality, not knowing which condition they would be randomized to, but aware that all could use the cybercycle after the three-month intervention. Volunteers aged 55 years or older were screened; exclusion criteria were known neurological disorders (e. g., Alzheimer's or Parkinson's) and functional disabilities that would significantly restrict participation in cognitive testing or exercise. Written physician approval was required. Union and Skidmore Colleges' institutional review boards approved the study; participants provided written informed consent. The study was registered with www.clinicaltrials.gov (NCT01167400). A priori sample size estimates were calculated based on published effect sizes for cognitive (d=.48)[8] and physiological (d=.41)[36] outcomes from physical exercise. An a priori power analysis had found that in a 2 x 2 (group x time) design, a sample of 100 would achieve .82 power to detect a significant effect (p=.05). At the time of study design when obtaining funding, individual randomization was planned and the need for cluster randomization was not foreseen; actual post hoc power is reported below in Results).

Interventions

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

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

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

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

Main Outcome Measures

Cognitive Assessment

Cognitive testing was done at enrollment (baseline), one month later (pre-intervention), and three months later (post-intervention). Analyses were conducted using pre- and post-scores. Baseline testing minimized the impact of practice and learning effects associated with serial assessments and provided a more stringent test of the main hypothesis.[38] Blinded ratings were achieved in most cases. The primary cognitive outcome of interest, executive function, was assessed via Color Trails 2-1 difference score (time to connect alternating color and number dots, minus time to connect only numbered dots),[39] Stroop C (time to name color of ink of contrasting color word),[40] and Digit Span Backwards (number of correct trials repeating a string of numbers in reverse order).[41] To reduce the number of statistical comparisons, an executive function composite score was obtained by converting raw scores on each test to Z-scores using the grand mean and standard deviation across both groups for each time point, then averaging the three measures (Cronbach 's α =.67). Timed tasks were reversed; a positive value on the composite indicates a score above the mean. Secondary cognitive outcomes were included to characterize the sample (e.g., clinical status below); no changes were expected on these tests (Suppl. TextFile2). At the completion of the study, participants' clinical status pre- and post-intervention was classified according to "typical" diagnostic criteria[43,44] for mild cognitive impairment (MCI; performance $\leq$ 1.5 *SD* on at least one subtest in the domains of executive function, verbal fluency, verbal memory, visuospatial skill, and visuospatial memory compared to normative data).[41] MCI incidence was comparable with prior research (Table 1).[45]

Physiological Assessment

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

Assessment of Exercise Behavior

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

Neuroplasticity Assessment

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

Statistical Analysis

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

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

<u>**Results**</u>

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

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

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

Planned simple effects analyses controlled for age, education, and cognitive performance at baseline, and revealed a significant increase in performance on the Color Trails Difference (*p*=.01) and Stroop C (*p* =.05) tests for cybercyclists, with no change for controls. Cybercyclists maintained a steady performance on Digits Backward, whereas the control group declined (*p* =.01). No significant interaction effects were found on physiological or secondary cognitive outcomes (Table 2). Analyses were repeated using age-matched and complete-case subsamples and results were similar (Suppl. Tables 1-4). No significant differences in exercise frequency, intensity or duration were found between the cybercyclists and controls (Table 3). While the average energy expended was relatively low (approximately 100 calories/ride), research has shown that even low-intensity exercise (100 calories) can serve as an adequate training stimulus among sedentary older adults.[47]

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

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

Biomarker Evidence of Possible Neuroplasticity: BDNF Results

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

Discussion

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

Contrary to expectations, effort and fitness did not appear to be the factors behind differential cognitive benefits found in the cybercycle group. There were no differences between the two groups on measures of exercise effort or physiological outcomes. Since this was a prescriptive intervention for both groups, and not a naturalistic study, it appears that participants in both groups were compliant with the regimen (similar goals were set and met), and further research is needed to evaluate whether naturalistic use would lead to greater effort by cybercyclists. These findings are consistent with some assertions in the literature that the cognitive benefit derived from exercise is not necessarily tied to fitness outcomes, although the debate continues.[47,48] Future research will be needed to tease apart the contributions of a variety of factors in the cybercycling condition. Consistency across conditions for goal setting and competition suggests virtual reality imagery and interactive decision-making might be the potent factors of the cybercycle. Exit interviews provided anecdotal evidence of the value of these unique features. Participants commented on their enjoyment of visual stimulation and the challenge of outpacing avatars. One 86 year-old noted she felt healthier and attributed this to actively maneuvering to "compete with that fellow ahead of me!" A 92 year-old participant noted, " It's fun to work with that screen and see the other bikers." Cybercycling provides a different experience than other cognitive stimulation such as television, since cybercyclists are interactively engaged.

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

Another explanation for the greater cognitive benefit found for cybercycling compared with traditional cycling could be that the effect is due to the *interactive* nature of combined physical and cognitive exercise. Perhaps cybercyclists benefit from a dual-exercise experience, accruing the positive effects of intertwined cognitive and physical exercise. When comparing average effect sizes in the literature, [52] controls demonstrate test-retest growth (.16), cognitive stimulation alone yields a comparable negligible effect (.13), physical exercise yields a small effect over-and-above controls (.32), while combined cognitive and physical exercise herein produced a medium effect over-and-above traditionally-exercising controls (.50). It is interesting that the combined effect of cognitive and physical exercise exceeds the sum of effects noted in the literature above, perhaps indicating a compounding or synergistic effect of cybercycling. Future research could evaluate this by comparing cognitive stimulation alone, physical exercise alone, and the combination of the two, as in many exergames. The exergame utilized herein, may allow the mind to be engaged in an interactive way with the physical challenge, perhaps providing a unique mechanism that fosters added cognitive benefit. Compounding cognitive benefit from a combined task does fit with the evolving understanding of the mechanisms of brain plasticity and the role of exercise and enriched environments in inducing angiogenesis, neurogenesis and other changes that foster neurovascular integrity.[15,54] A combined effect would be consistent with the animal literature, where cognitive benefit from physical exercise and mental stimulation have been found to occur by different mechanisms (cell proliferation and cell survival, respectively).[54-56] This combined-effect hypothesis expands upon prior research in humans, which has found enhanced cognitive benefits of physical and cognitive exercise interventions administered in tandem.[57-58] Similarly, these findings fit with prior research that indicates cognitive benefit over and above traditional exercise, from physical exercise that is cognitively challenging (e.g., Tai Chi or dancing).[59-61] No previous research has examined the possibility of added cognitive benefit of simultaneous, interactive cognitive and physical exercise in a controlled trial, where the physical motions are the same, but the mental challenge is experimentally controlled.

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

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

Limitations of this study include unequal representation of age and education in the groups despite randomization, and while statistical controls were employed and age- and education-matched post hoc analyses were conducted, future research could prospectively match on these variables. Also, participants had a relatively high level of education and ethnic variability was limited; additional research is needed to test generalizability. Non-completers performed worse on some cognitive and physiological measures, thus screening for minimum levels of function may be advisable.

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

Follow-up studies could aim to replicate prior research by using neuroimaging to examine the impact of exergaming on brain volume in key regions (e.g., anterior cingulate cortex and hippocampus), for further evidence of neuroplasticity.[13-16] With a refined experimental design, future research could clarify if cognitive exercise alone is sufficient to produce the observed cognitive change, or if exergaming leads to added benefit by compounding or synergistic neurophysiological advantages when mental challenges are linked to physiological movements. Another interesting follow-up study would compare outdoor street-cycling with cybercycling, since the natural world, street obstacles, other cyclists, and way-finding would also create cognitive challenge. Safety and seasonal factors would pose challenges, but it would be interesting to evaluate biophilia factors, degree of cognitive stimulation, and social presence. Additionally, more could be done to control related factors on a cybercycle; some labs have full-surround audio-visual virtual reality environments, that could allow controlled testing of "outdoor" f actors while yet ensuring safety,[66] Last, a cost-benefit analysis of this type of intervention needs to be explored and evaluated in light of reports that physical activity interventions for inactive older adults can be cost-effective.[67]

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

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References

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

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

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

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

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TABLE 2. Neuropsychological and Physiological Outcomes After Three Months of Exercise (Intent-to-Treat Analysis).

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

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

Note: Cybercyclists represented by solid line; control cyclists represented by the dashed line; n=79; mixed linear model (random effects: age, education, and cluster) group x time interaction significant (p=.002).

Table

TABLE 1. Baseline Characteristics of Trial Participants

	cybercycle (n = 38)		control bike (n = 41)	
Age, mean (SD), y[1]	75.7	(9.9)	81.6	(6.2)
Women, No. (%)	33	(70.7)	29	(86.8)
Education, mean (SD), y[1]	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[2]	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 (≥ 1 domain: ≤ -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.

[1] Group difference at baseline on age (*p* = .002) and education (*p* < .001).

[2] Physical activity level (daily kcal) was estimated in Year 1 via questionnaire and Year 2 via Actical (see Methods).

Table

TABLE 2. Neuropsychological and Physiological Outcomes After Three Months of Exercise (Intent-to-Treat Analysis)[a]	Mean Difference From Baseline (95% CI) Cybercycle (n = 38)	Mean Difference From Baseline (95% CI) Control Bike (n = 41)	*p* (Degrees of Freedom) ANCOVA Repeated Measures Group x Time[b]
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[c]:			
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^{-1}	-2.96 (-3.00 to -2.92)	11.09 (11.05 to 11.13)	.04 (1, 71)
Leg Flex 60°, s^{-1}	-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.

[a] Marginal mean differences and CIs reported based on repeated measures ANCOVA controlling for age and education.

[b] The first degree of freedom in parentheses refers to the effect (group x time) and the second refers to the error term.

[c] No significant changes expected given prior research literature.

Table

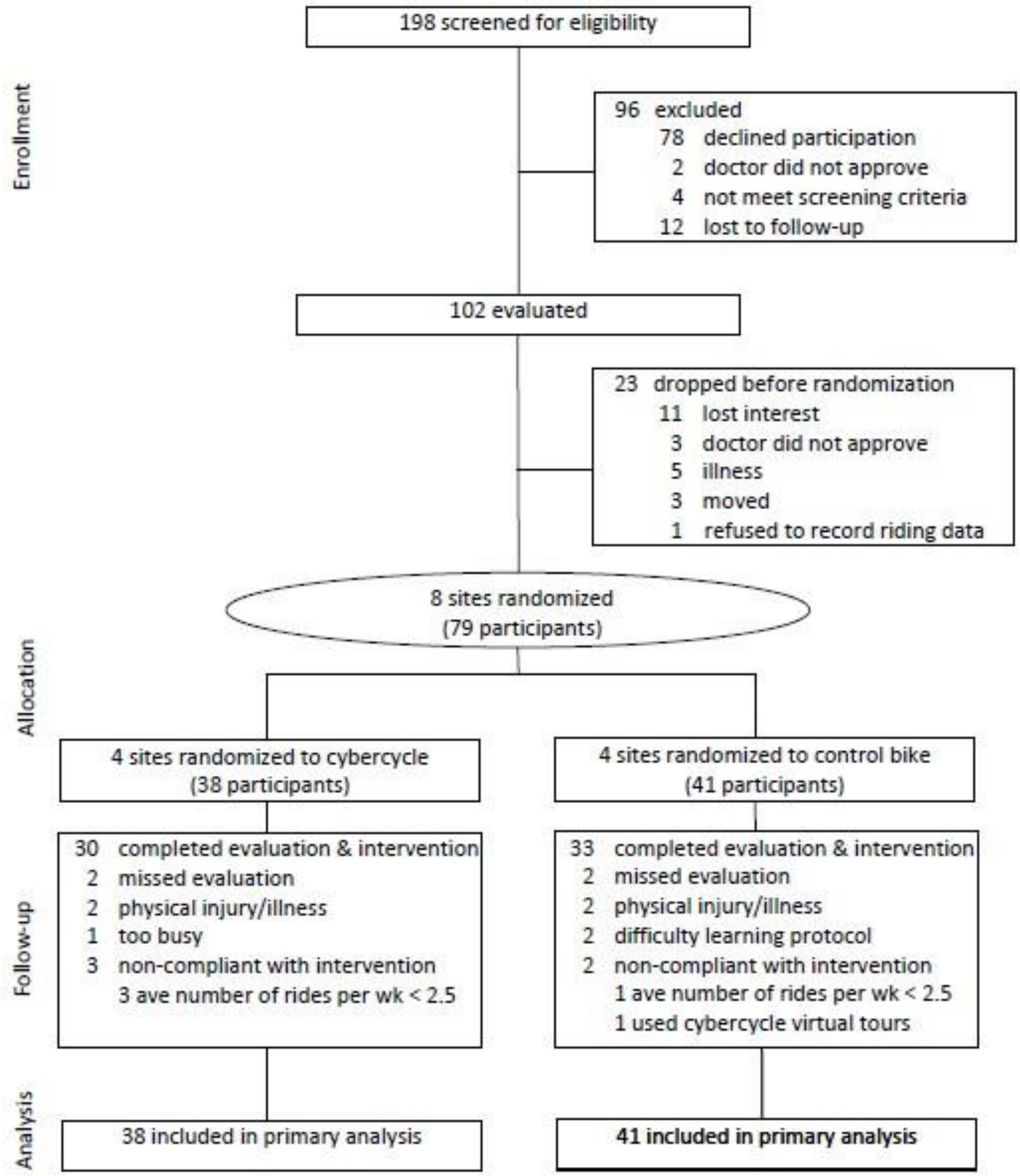
TABLE 3. Exercise Behavior Outcomes After Three Months of Exercise: Cybercycle vs. Control Bike[a]

	Mean (SD) Cybercycle (n = 30)		Control Bike (n = 33)		Difference Between Interventions Mean, (95% CI)	P Value (Degrees of Freedom)
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[b]	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[b]	7.4	(0.38)	8.3	(0.37)	-0.83 (-0.86 to -0.80)	.19 (1, 31)
Speed Peak, mph[b]	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)

[a] Marginal means and SDs reported based on ANCOVA controlling for age and education.

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

Figure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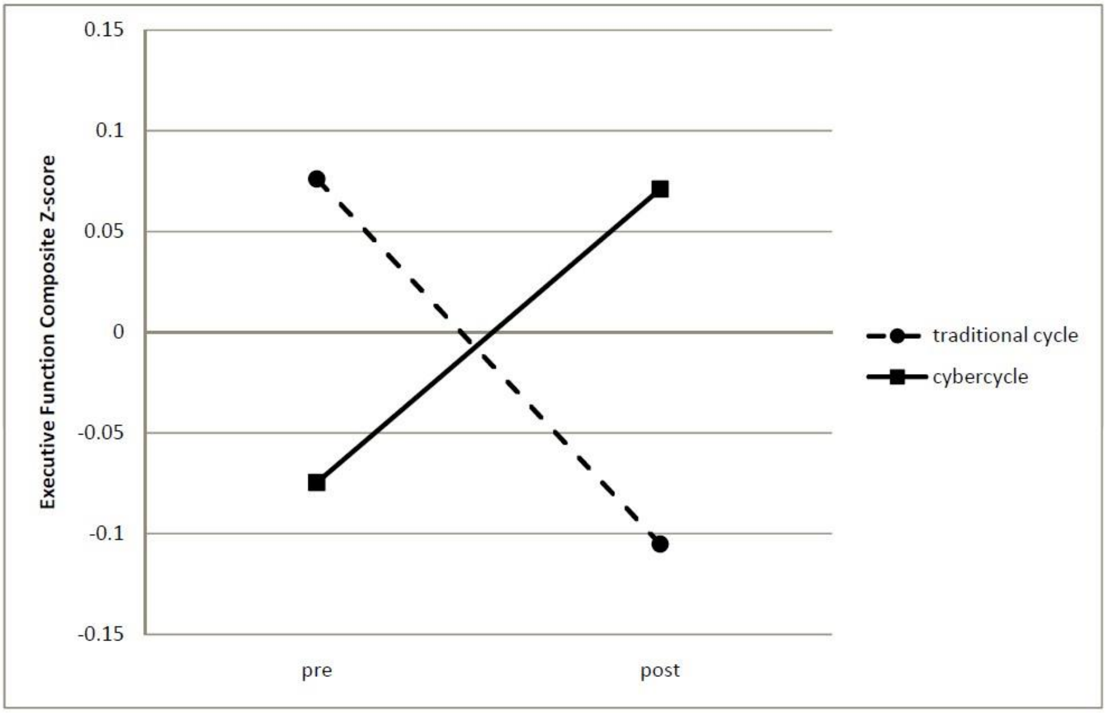
Enrollment
96 excluded
78 declined participation
2 doctor did not approve
4 not meet screening criteria
12 lost to follow-up
102 evaluated
23 dropped before randomization
11 lost interest
3 doctor did not approve
5 illness
3 moved
1 refused to record riding data
8 sites randomized
(79 participants)
Allocation
4 sites randomized to cybercycle
(38 participants)
4 sites randomized to control bike
(41 participants)
Follow-up
30 completed evaluation & intervention
2 missed evaluation
2 physical injury/illness
1 too busy
3 non-compliant with intervention
3 ave number of rides per wk < 2.5
33 completed evaluation & intervention
2 missed evaluation
2 physical injury/illness
2 difficulty learning protocol
2 non-compliant with intervention
1 ave number of rides per wk < 2.5
1 used cybercycle virtual tours
Analysis
38 included in primary analysis
41 included in primary analysis

Figure


0.15
0.1
0.05
0
-0.05
-0.1
-0.15
Executive Function Composite Z-score
pre
post
traditional cycle
cybercycle

Figure

Content of the Supplemental Online Materials

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

TABLE 1. Neuropsychological and Physiological Outcomes: Age and Education-Matched[a]

	Mean Difference From Baseline (95% CI)		P (Degrees of Freedom) ANCOVA
	Cybercycle (n = 26)	Control Bike (n = 26)	Repeated Measures Group x Time[b]
Primary Cognitive Outcomes:			
Executive Function			
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)
Secondary Cognitive Outcomes[c]:			
Attention			
LDST, sum score	1.22 (-1.11 to 3.56)	0.90 (-1.55 to 3.35)	.77 (1, 46)
Verbal Fluency			
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)
Verbal Memory (immediate)			
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)
Verbal Memory (delayed)			
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)
Visuospatial Skill			
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)
Visuospatial Memory (delayed)			
Figure Delayed Recall, score	0.46 (-1.58 to 2.49)	2.90 (0.72 to 5.08)	.11 (1, 45)
Motor Function			
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)
Physiological Outcomes:			
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^{-1}	-2.06 (-12.66 to 8.54)	14.91 (3.98 to 25.84)	.05 (1, 46)
Leg Flex 60°, s^{-1}	-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.

[a] Marginal means and SDs reported based on repeated measures ANCOVA controlling for age and education.

[b] The first degree of freedom in parentheses refers to the effect (group x time) and the second refers to the error term.

[c] No significant changes expected given prior research literature.

[d] 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[a]

	Mean (SD)				Difference Between Interventions	P Value (Degrees
	Cybercycle (n = 30)		Control Bike (n = 33)		Mean, (95% CI)	of Freedom)
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[b]	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[b]	7.4	(0.38)	8.3	(0.37)	-0.83 (-0.86 to -0.80)	.19 (1, 31)
Speed Peak, mph[b]	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)

[a] Marginal means and SDs reported based on ANCOVA controlling for age and education.

[b] 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)		Non-Completers (n = 8)		*p* Value	Completers (n = 33)		Non-Completers (n = 8)		*p* 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)[a]

	Mean Difference From Baseline (95% CI)		*p* (Degrees of Freedom) ANCOVA
	Cybercycle (n = 30)	Control Bike (n = 33)	Repeated Measures Group x Time[b]
Primary Cognitive Outcomes:			
Executive Function			
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)
Secondary Cognitive Outcomes[c]:			
Attention			
LDST, sum score	0.88 (0.65 to 1.11)	0.55 (0.33 to 0.77)	.78 (1, 57)
Verbal Fluency			
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)
Verbal Memory (immediate)			
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)
Verbal Memory (delayed)			
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)
Visuospatial Skill			
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)
Visuospatial Memory (delayed)			
Figure Delayed Recall, score	0.12 (0.38 to -0.14)	1.99 (2.25 to 1.74)	.27 (1, 56)
Motor Function			
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)
Physiological Outcomes:			
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^{-1}	-2.85 (-2.72 to -2.98)	12.15 (12.28 to 12.02)	.06 (1, 56)
Leg Flex 60°, s^{-1}	-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.

[a] Marginal means and SDs reported based on repeated measures ANCOVA controlling for age and education.

[b] The first degree of freedom in parentheses refers to the effect (group x time) and the second refers to the error term.

[c] No significant changes expected given prior research literature.

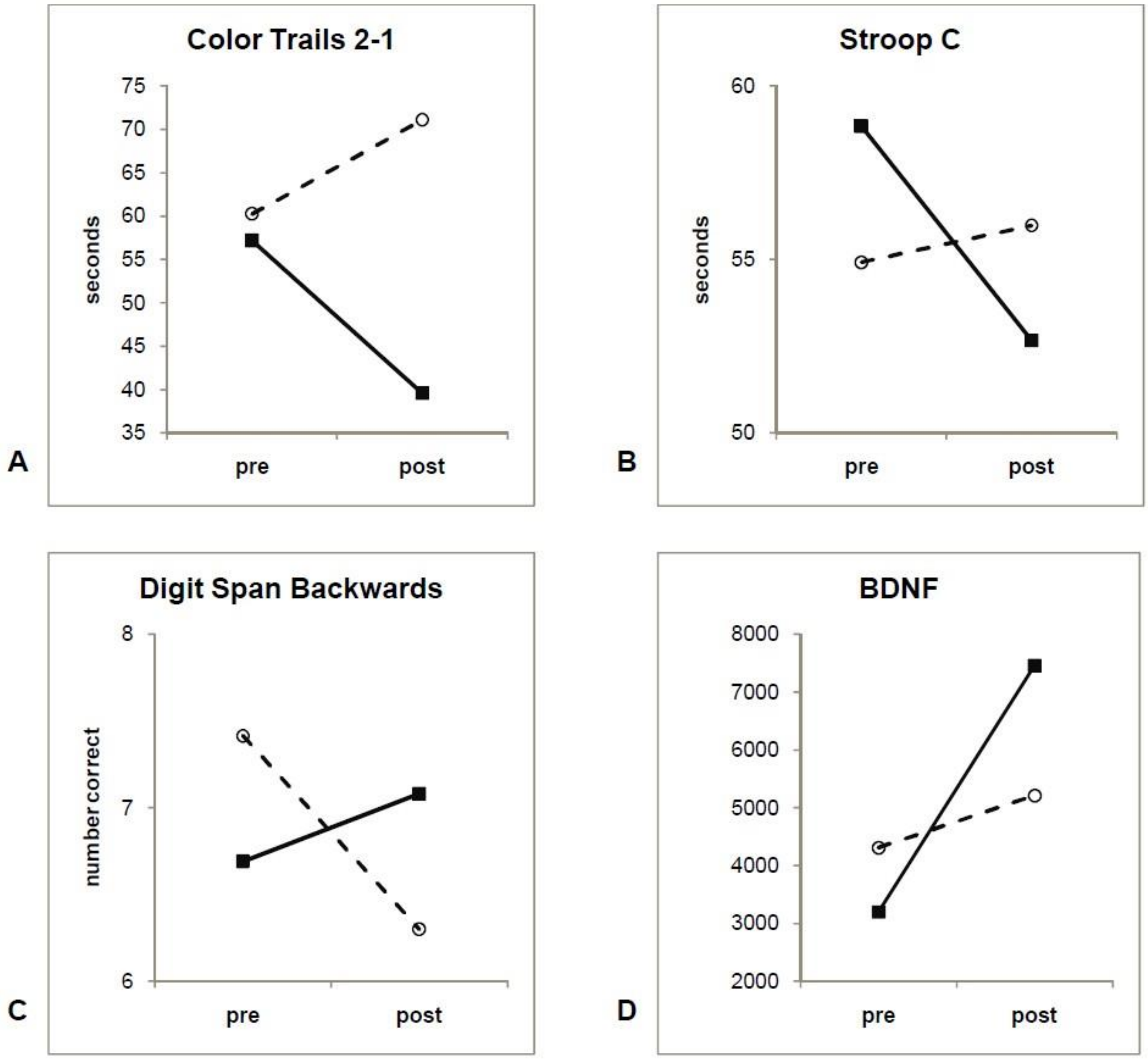
[d] Sample sizes: cybercycle (n = 14) and control bike (n = 17) due to missing biomarker data.

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[a]	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[a]	

[a] 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 Netathalon 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 Expresso 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),[1] Stroop C (time to state the ink color while suppressing the contrasting typed color name),[2] and Digit Span Backwards (number of correct trials repeating a string of numbers in reverse order).[3]

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

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, 3rd 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 $pg \cdot ml^{-1}$ 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 spectophotometric plate reader (BioTek, Winooski, VT).