Review article

The impact of exercise in improving executive function impairments among children and adolescents with ADHD, autism spectrum disorder, and fetal alcohol spectrum disorder: a systematic review and meta-analysis

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Abstract

Objective: he goal of this work was to perform a systematic review and meta-analysis evaluating and comparing exercise related improvements in various executive function (EF) domains among children and adolescents with attention-deficit hyperactivity disorder (ADHD), Autism Spectrum Disorders (ASD), and Fetal Alcohol Spectrum Disorders (FASD). **Methods:** A systematic literature research was conducted in PubMed, CENTRAL, and PsycInfo from October 1st, 2018 through January 30th, 2019 for original peer-reviewed articles investigating the relationship between exercise interventions and improvements in three domains of executive function (working memory, attention/set shifting, and response inhibition) among children and adolescents with ADHD, ASD, and FASD. Effect sizes (ES) were extracted and combined with random-effects meta-analytic methods. Covariates and moderators were then analyzed using meta-regression and subgroup analyses. **Results:** A total of 28 studies met inclusion criteria, containing information on 1,281 youth (N=1197 ADHD, N= 54 ASD, N=30 FASD). For ADHD, exercise interventions were associated with moderate improvements in attention/set-shifting (ES 0.38, 95% CI 0.01-0.75, k=14) and approached significance for working memory (ES 0.35, 95%CI -0.17-0.88, k=5) and response inhibition (ES 0.39, 95%CI -0.02-0.80, k=12). For ASD and FASD, exercise interventions were associated with large improvements in working memory (ES 1.36, 95%CI 1.08-1.64) and response inhibition (ES 0.78, 95%CI 0.21-1.35) and approached significance for attention/set-shifting (ES 0.69, 95% -0.28-1.66). There was evidence of substantial methodologic and substantive heterogeneity among studies. Sample size, mean age, study design, and the number or duration of intervention sessions did not significantly moderate the relationship between exercise and executive function. **Conclusion:** Exercise interventions among children and adolescents with neurodevelopmental disorders were associated with moderate improvements in executive function domains. Of note, studies of youth with ASD and FASD tended to report higher effect sizes compared to studies of youth with ADHD, albeit few existing studies. Exercise may be a potentially cost-effective and readily implementable intervention to improve executive function in these populations.

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Introduction

Neurodevelopmental disorders, specifically attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and fetal alcohol spectrum disorders (FASD) affect approximately 1 out of 6 children in the United States[1]. ADHD has a high co-occurrence in children and adolescents with FASD and ASD, with prevalence estimates consistently over 50%-60%[2,3]. Executive function (EF), which refers to higher order cognitive processes that are responsible for purposeful goal-directed behavior[4], is frequently compromised in children with ADHD, ASD, and FASD and is implicated in associated behavioral, socio-emotional, and cognitive impairments[5].

Although stimulants remain the gold standard for treatment of EF deficits associated with ADHD, up to 30% of children do not show a beneficial response to stimulants[6-8]. Response to stimulants is even further reduced in children and adolescents with co-morbid autism or prenatal alcohol exposure (PAE)[6-8]. Furthermore, there is evidence that stimulants have a greater effect on certain EF measures such as attentional performance, and less of an effect on measures such as impulsivity[9]. Behavioral treatments are relatively difficult to implement, costly, and effects are hard to maintain after termination of treatment[10]. Research shows that as children with PAE mature, they exhibit problems with the misuse of alcohol, with estimates of prevalence rates ranging from 35% to 60%[11]. Therefore, new approaches to differentiate and treat the spectrum of EF impairments in children with ADHD, FASD, and ASD are needed.

In recent years, a growing body of literature has supported the growing role of exercise in improving cognition, notably EF[12-14]. Many converging lines of research into the biological underpinnings of exercise-based improvements in EF have been elucidated. Exercise has been shown to increase levels of norepinephrine, dopamine, and serotonin in the prefrontal cortex, hippocampus and striatum to affect mood and cognition[15,16]. It is posited that, as a result of exercise, increased levels of dopamine enhance attention, focus, and learning, whereas increases in norepinephrine improve executive function, reduce distractibility, modulate arousal, and enhance memory to assist in learning[17,18]. In animal models, exercise has been shown to reduce oxidative stress and improve neuroendocrine auto-regulation which has been shown to counteract stress and age-related neuronal degeneration[19]. Exercise has also been shown to directly cause morphological changes in the brain by increasing blood flow, and has also been shown to result in upregulation of brain-derived neurotrophic factor (BDNF), which plays an integral role in hippocampal functioning and long term potentiation for learning and memory, synaptic plasticity, neurogenesis, and neuroprotection[20].

Exercise appears to improve EF in children and adolescents with attention-deficit/hyperactivity disorder (ADHD)[14,21,22]. Aerobic

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exercise interventions of at least 30 minutes show the most promise in improving EF deficits associated with ADHD[22]. Research provides further evidence that exercise induces improvements in executive function (EF) in children and adolescents with ADHD, more so than in typically developing children[14,21,22]. Although studies suggest that exercise induces similar improvements in EF in animal models exposed prenatally to alcohol, research evaluating the impact of exercise in EF in children and adolescents with prenatal alcohol exposure is lacking. To this date, there is only one study evaluating effectiveness of an exercise intervention on EF in children and adolescents with prenatal alcohol exposure[23]. Furthermore, research investigating whether exercise interventions have beneficial effects on some EF domains in children with neurodevelopmental disorders is lacking[24].

The purpose of this systematic review and meta-analysis is to 1) examine potential differences in exercise related improvement in EF outcomes in different neurodevelopmental disorders, specifically ADHD, FASD, and ASD; 2) evaluate whether certain EF domains are more sensitive to the effects of exercise in children and adolescents with ADHD, FASD, and ASD; and 3) explore whether specific characteristics of participants or the exercise interventions can predict the magnitude of EF improvement in children and adolescents with ADHD, FASD, and ASD. To our knowledge, this is the first meta-analysis of existing studies investigating and comparing the effects of exercise on EF subdomains in children and adolescents with ADHD, FASD, and ASD.

Methods

Search strategy

A systematic literature review was performed using PubMed, CENTRAL, the Cochrane Collaboration database of controlled trials (in the Cochrane Library), and PsycInfo from October 1st, 2018 through January 30th, 2019. Keywords used in the search included (autism OR ADHD OR fetal alcohol exposure OR Fetal Alcohol Spectrum Disorders) AND (exercise OR physical activity OR physical fitness) AND (executive function tests OR executive function OR common neuropsychological measures of executive function). Search strategy was based on previous systematic reviews looking at executive function deficits in FASD and ADHD and can be found in the supplemental materials[5]. Reference lists of included manuscripts and related prior review articles were reviewed for additional studies[13,22,24-30].

Study selection

The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines and adhered to protocol defined prior to data extraction. Only peer-reviewed English-language journal articles were included. The following additional inclusion criteria were applied: study participants 0-18 years old, the study participants were diagnosed with ADHD, ASD, or FASD, the study tested the effect of an exercise intervention on EF, the study used individual neuropsychological assessment tasks as an outcome measure. Studies were excluded if the study did not report an effect size, or statistic from which an effect size could be computed (i.e. book chapters, qualitative reviews). The following exclusion criteria were applied: the study measured domains of cognition other than executive function, the study did not report a measure of executive function directly obtained by assessment of the child (i.e. studies that relied on parent or teacher report), the study did not test the effect of an exercise intervention (i.e. observational studies). The literature search, title, and abstract screening, and evaluation of inclusion and exclusion criteria were performed independently by two of the study's authors, with disagreements resolved via consensus ratings.

Data extraction

Effect sizes were extracted when the effect size measured the relationship between exercise intervention and executive function. If an effect size was not reported, data from which an effect size could be calculated (e.g. means and standard deviations) was extracted. Measures of executive function were divided into the following domains: working memory, attention/set-shifting, and response inhibition. When more than one domain was reported, a separate effect size was extracted (or calculated) for each domain.

Measures of attention/set shifting included the following: Wisconsin Card Sorting Test, Cognitive Battery Test (a mixed measure of Paced serial addition, size ordering, listening span, digit span backwards, and visual coding), the Color Trails Test Part 1, the Trail Making Test, Eriksen Flanker Test, Test of Everyday Attention, Connor's Continuous Performance Test, the Visual Pursuit Test, Task Switching Paradigm, and the Auditory Oddball Test. Measures of working memory included the following: Digit Span, Digit Symbol Test, Visual Sequential Memory Test, Corsi Block Tapping Test, and Automated Working Memory Assessment Test. Measures of response inhibition included the following: Stroop Color and Word Test, Go/No Go Test, Determination Test, Stop Signal Task, STOPIT Task, and Children's Color Trails Test Part 2. The following data were extracted from each study when reported: participant characteristics including diagnosis, mean age, and stimulant medication use; sample size; study year; study design (crossover, parallel, or single-group pretest-posttest); duration of exercise intervention (i.e. one-time exercise vs weekly exercise); exercise intensity (low vs moderate or high intensity); and type of exercise (running, cycling, mixed exercises, or other). Moderate or High intensity exercise was defined by exercise that reaches at least 50% of the maximal heart rate as defined by the American College of Sports Medicine (ACSM) guidelines[31].

Data analysis

As studies reported different measurement methods, standardized mean different estimates of difference in executive function domain scores were used as effect size (ES) estimates. ES estimates were converted to Hedges' g to provide an unbiased ES adjusted for small sample sizes. An ES of 0.2 is considered to be low, 0.5 moderate, and 0.8 large[32]. The 95% Confidence Interval for each ES was also calculated. The ES of each executive function domain represents the average ES estimate derived from each of its relevant neuropsychological measures. At least three independent datasets had to be available to calculate a summary ES. The DerSimonian-Laird (D-L)[33] random effects method of meta-analyses was used to pool effect size estimates. This method accounts for variability between studies and allows for generalization of results beyond the sample population[34]. Each domain of EF (attention/set shifting, working memory, and response inhibition) was pooled separately. Between-study heterogeneity was assessed with the I2 statistic and Cochran's Q. Confidence intervals were inspected for each pooled SMD and regression coefficient to evaluate the interval estimate of each population parameter. To assess for possible impact of continuous covariates on effect measures, meta-regression was performed on effect size estimates on sample size N, mean age, and year of study publication. A covariate was investigated using meta-regression when at least three independent datasets provided data on the potential moderator. Begg's and Egger's tests[35,36], were conducted to assess for publication bias and funnel plots were visually inspected. Statistical Analyses were carried out in STATA Version 15.1 (College Station, TX: StataCorp, LLC). P-values were two-tailed, and an alpha level of 0.05 conferred statistical significance. The study did not meet criteria for IRB review.

Subgroup analyses

To ascertain potential sources of heterogeneity between studies, subgroup meta-analyses were performed to further evaluate sources of variability. Between-study heterogeneity within subgroups was assessed using the I2 statistic. Subgroup analyses were conducted for categories for which sufficient data was reported (k > or equal to 2). The following subgroups were assessed: (1) duration (single vs multiple session intervention), (2) intensity (moderate or high vs low), (3) type of exercise intervention (running, cycling, mixed, and other), and (4) study design (repeated measures vs intervention/control).

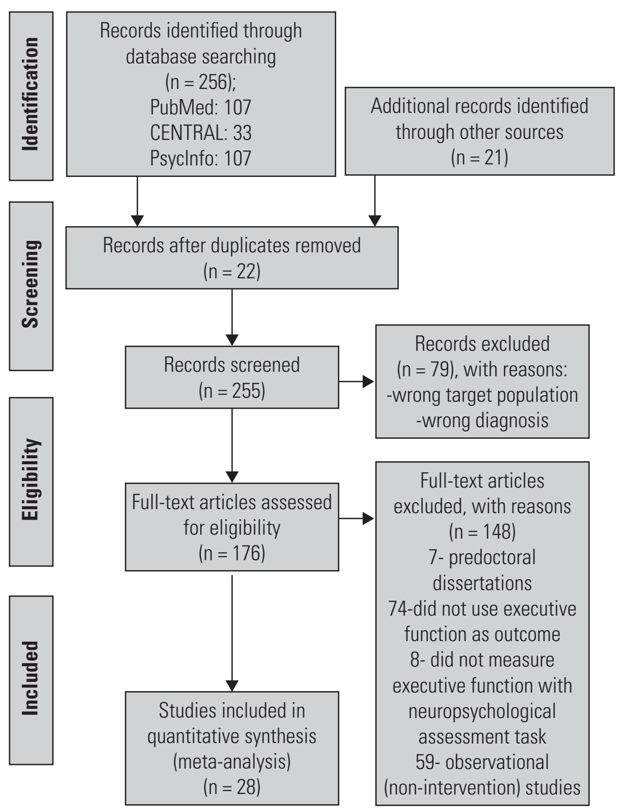

Figure 1. PRISMA Flowchart depicting study search and selection process. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

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Results

A total of 256 potentially relevant studies were retrieved, including 107 from PubMed, 39 from CENTRAL, and 110 from PsycInfo. After duplicates were removed, the titles and abstracts of 255 references were assessed for eligibility. Of these, 79 were excluded, and 176 full-text articles were screened. Finally, 28 studies met eligibility criteria, of which 23 assessed children with ADHD, four studies assessed ASD, and one study assessed FASD. Due to the relatively small number of ASD and FASD studies, these studies were combined. The study inclusion (PRISMA) flow chart is displayed in Figure 1.

ADHD and exercise

The total number of participants in the selected studies was 1,197. The number of participants per study varied from 12[37] to 552[38]. Exercise interventions varied in terms of frequency, intensity, and type of exercise (refer to Table 1). Detailed characteristics on the included studies are presented in Table 1.

Attention and set-shifting

Fourteen studies investigated the relationship between exercise interventions and attention and set-shifting scores. Of these, 5 studies reported scores pre- and post-exercise intervention and pre- and post-control intervention[21,39-42], three studies reported post-exercise intervention and post-control intervention scores only[43-45], and 1 study reported pre- and post-exercise intervention scores only[46]. Five studies included a healthy (non-ADHD) control group[38,43,47-50].

The overall pooled ES was 0.38 (95% CI 0.01-0.75, k = 14) (Figure 2). The I^2 test of heterogeneity was statistically significant (I^2 = 99.7%, df = 13, p < 0.01), and thus subgroup analyses were conducted to identify substantive and methodological sources of heterogeneity. Type of exercise was a significant moderator of ES, wherein studies that involved running as the exercise intervention tended to find more robust ES (g = 0.49, 95% CI 0.12-0.86, k = 5) compared to other types of exercise (cycling: g = 0.16, 95% CI -0.41-0.72, k = 3; mixed exercises: g = 0.19, 95% CI -0.17-0.55, k = 2; other: g = 0.50, 95% CI -0.34-1.33, k = 4). Meta-regression analyses suggested that participant age and year of study publication were not significant predictors of ES. Subgroups analyses found that presence of healthy control group, study design, duration, intensity, and comorbid medication were not significant moderators of ES. Egger's test demonstrated evidence of publication bias (t(13) = -2.43, p = 0.032), wherein smaller studies tended to report stronger associations between exercise intervention and improvement in attention and set-shifting scores.

Working memory

Five studies investigated the relationship between exercise interventions and working memory scores. Of these, four studies reported scores pre- and post-exercise intervention and pre- and post-control intervention[39,40,51,52]. One study reported post-exercise and post-control scores only[53]. The overall pooled ES was 0.35 (95% CI -0.17-0.88, k = 5) (Figure 2). The I^2 test of heterogeneity was statistically significant (I^2 = 99.5%, df = 4, p < 0.01). Meta-regression analyses suggested that study size, participant age and year of study publication were not significant predictors of ES. Subgroup analyses were limited due to small number of total studies. Begg's and Egger's tests, as well as visual inspection of the funnel plot, did not demonstrate evidence of publication bias.

Response inhibition

Twelve studies investigated the relationship between exercise interventions and response-inhibition scores. Of these, nine studies reported scores pre- and post-exercise intervention and pre- and post-control intervention, two studies reported post-exercise intervention and post-control intervention scores only[54,55] and one study reported pre- and post- exercise scores only[46]. Only one study included a healthy (non-ADHD) control group[49].

The overall pooled ES was 0.39 (95% CI -0.02-0.80, k = 12) (Figure 2). The I^2 test of heterogeneity was statistically significant (I^2 = 99.5%, df = 11, p < 0.01), and thus subgroup analyses were conducted to identify substantive and methodological sources of heterogeneity. Meta-regression analyses suggested that study size, participant age and year of study publication were not significant predictors of ES. Subgroup analyses suggested that studies including participants taking co-morbid ADHD medication tended to report higher ES of the relationship between exercise interventions and response inhibition scores (with comorbid medications: ES 0.50, 95% CI 0.17-0.82; without comorbid medication ES 0.28, 95% CI -0.46-1.03). Presence of healthy control group, study design, duration, intensity, and type of exercise were not significant moderators of ES. Begg's and Egger's tests, as well as visual inspection of the funnel plot, did not demonstrate evidence of publication bias.

Table 1.

Study			Sample characteristics				Intervention			Findings		
Author	Pub Year	Study design	Co-morbid stimulant medication	Sample Size	Age range (M+\- SD)	Diagnosis	Type	Intensity	Duration	EF Measure	EF Domain	Key Result
Chang	2012	Parallel group	Yes	40 (3 female, 37 male)	10.43+/-0.90	ADHD	Running	Moderate-high intensity	30 minutes on treadmill (5 min warmup, 5 minute cooldown, 20 minute run)	Stroop Test, Wisonsin Card sorting Test (WCST)	Stroop Test: response Inhibition; WCST: attention/set shifting	Greater improvement in non perseverative errors of WCST and Stroop Color-Word Test in exercise group compared to controls
Pritchard	2018	Crossover wait-list control study	Not reported	30 (14 boys, 16 girls)	10.2 (+/- 0.4 years)	FASD	Mixed (FAST club intervention program)	Unreported	8 week duration (two 1.5 hr sessions per week)	Children's Color Trails Test (CCTT)	CCTT 1: attention/ set shifting; CCTT 2: response inhibition	Greater improvement in exercise group post-intervention vs pre-intervention
Chang	2014	Crossover wait-list control study	Yes	27 (23 male, 4 female)	age 5-10	ADHD	Aquatic exercise	Moderate-high intensity	8 week duration (two 1.5 hr sessions per week)	Go/No go Task	Response inhibition	Greater improvement in accuracy on No/ go task scores in exercise group compared to controls
Hill	2011	Crossover wait-list control study	Not reported	552 (295 male, 257 female)	age 8-12	ADHD	Mixed (jogging and jumping)	Moderate-high intensity	I:exercise intervention for week 1; C: no exercise for week 1. Exercise was 10-15 minutes daily	Paced Serial Addition, Size Ordering, Listening Span, Visual Coding, Digit Span	Paced Serial Addition, Size Ordering, Listening Span, Visual Coding: attention/set shifting; Digit Span: working memory	Exercise group outperformed non exercise group by week 2
Kang	2011	Parallel group	Yes	28	ages 7-9	ADHD	Running	Moderate-high intensity	6 week duration (2 1.5 hr sessions per week)	Digit Symbol Test and Trail Making Test Part B	Digit Symbol Test: working memory; and Trail Making Test: attention/set shifting	Greater improvement in Digit Symbol Test, and TMT-Part B scores in exercise group compared to controls
Pontifex	2012	Crossover	No	20 (14 male, 6 female)	ages 8-10	ADHD	Running	Moderate-high intensity	20 minute session	Eriksen Flanker Test	Attention/set shifting	Greater improvement in response accuracy and improvement in post-error slowing in exercise group compared to controls
Verret	2012	Parallel group	Yes	21 (19 male, 2 female)	9.1 (+/- 1.1)	ADHD	Mixed (basketball, soccer)	Moderate-high intensity	10 week duration (3 45 minute sessions per week)	Test of Everyday Attention for children	Attention /set shifting	Improvements in attention and informational processing in exercise group compared to controls

Study			Sample characteristics				Intervention			Findings		
Author	Pub Year	Study design	Co-morbid stimulant medication	Sample Size	Age range (M+\- SD)	Diagnosis	Type	Intensity	Duration	EF Measure	EF Domain	Key Result
Medina	2010	Single group	Yes	25 (all males)	9.33 +/-2.87	ADHD	Running	Moderate-high intensity	30 minute session	Conner's Continuous Performance Test-II	Attention/set shifting	Improvement in attention measures in exercise group compared to controls
Mahon	2013	Parallel group	Yes	43 (30 male,13 female)	age 8-14	ADHD	Cycling	Moderate-high intensity	10 minute session	Conner's Continuous Performance Test-II (CCPT II)	Attention/set shifting	No significant improvement in CCPT II scores in either ADHD or healthy control group following exercise
Craft	1983	Single group	No	31 (all males)	ages 7-10	ADHD	Cycling	Unreported	10 minute session	Digit Span, visual sequential memory	Working memory	No improvement in working memory post-intervention vs pre-intervention
Anderson-Hanley	2011	Single group	Not reported	12 (8 boys, 4 girls)	14.8 +/-2.7	ASD	Other (dance)	Unreported	20 minute session	Digit Span, Color Trails Test, Stroop Task	Digit span: working memory; Color Trails Test: inhibition and attention/set shifting; Stroop Task: response inhibition	Improvement in 1 measure of digit span (digit backwards) post-intervention vs pre-intervention
Anderson-Hanley	2011	Single group	Not reported	10 (all males)	13.2 +/- 3.8	ASD	Cycling	Unreported	20 minute session	Digit Span, Color Trails Test, Stroop Task	Digit span: working memory; Color Trails Test: inhibition and attention/set shifting; Stroop Task: response inhibition	Improvement in 1 measure of digit span (digit backwards) post-intervention vs pre-intervention
Choi	2014	Parallel group	Yes	30 (all males)	15.9 +/-1.2	ADHD	Mixed (running, jumping, basketball)	Moderate-high intensity	6 week duration (3 90 minute sessions per week)	Wisconsin Card Sorting Test (WCST)	Attention/set shifting	Greater improvement in perseverative errors of WCST in exercise group compared to controls
Gawrilow	2016	Single group	Yes	47 (all males)	14.37+/-1.88	ADHD	Other (trampoline)	Unreported	5 minutes	Go no task	Response inhibition	Improvement in response inhibition in exercise group compared to controls
Ziereis	2014	Crossover wait-list control study	No	43	9.45 +/-1.43	ADHD	Mixed (acrobatics, balance training, coordinative exercises, etc)	Unreported	12 week duration (60 minute sessions)	Digit span, letter number sequencing task of HAWIK-IV, Corsi blocking tapping test	Working memory	ignificant improvement in all working memory measures seen after 12 weeks in exercise groups, though no effects were seen after one week in either group
Chou	2017	Parallel group	No	49 (38 males, 11 females)	age 8-12	ADHD	Other (yoga)	Moderate-high intensity	8 week duration (2 40 min sessions per week)	Visual pursuit test of the vienna test system	Visual pursuit test: attention/ set shifting determination test: response inhibition	Improvements seen in both EF measures in yoga group compared to controls

Study			Sample characteristics				Intervention			Findings		
Author	Pub Year	Study design	Co-morbid stimulant medication	Sample Size	Age range (M+\- SD)	Diagnosis	Type	Intensity	Duration	EF Measure	EF Domain	Key Result
Memarmoghaddam	2016	Parallel group	No	40 (all males)	8.31+/-1.29	ADHD	Mixed (table tennis, football, basketball, etc)	Moderate-high intensity	8 week duration (3 90 min sessions per week)	Go/no Go Task, Stroop Task	Response inhibition	Significant improvement seen in exercise group post-intervention vs pre-intervention
Hung	2016	Single group	No	34 (33 males, 1 female)	10.24+/-1.78	ADHD	Running	Moderate-high intensity	30 minute session	Task switching paradigm (Dai et al 2013)	Attention/set shifting	Improvement in task switching in exercise group compare to controls
Gelade	2017	Parallel group	No	37 (28 male, 9 female)	9.8 +/-1.96	ADHD	Other (not mentioned)	Moderate-high intensity	10-12 week duration (3 sessions per week)	auditory oddball task, SST, visual spatial working memory task	AOT:attention/ set shifting; SST: response inhibition; visual spatial WM task: working memory	Improvement found for working memory in exercise group compared to controls
Pan	2017	Crossover wait-list control study	Not reported	22 (all boys)	age 6-12	ASD	Other (table tennis)	Unreported	12 week duration (2 70 min sessions per week)	Wisconsin card sorting test (WCST)	Attention/set shifting	Significant improvement in total correct, perseverative response, and conceptual -level response subscores of WCST post-intervention vs pre-intervention
Pan	2016	Crossover study	Yes	32 (all males)	8.93+/-1.49	ADHD	Other (racket sport)	Moderate-high intensity	12 week duration (2 70 min sessions per week)	Stroop Test	Response inhibition	Significant improvements seen in response inhibition post-intervention vs pre-intervention
Bustamente	2016	Parallel group	Yes	19	age 6-12	ADHD	Mixed (modified sports, jumprope, etc)	Unreported	10 week duration (5 60 min sessions per week)	STOPIT task, and automated working memory assessment (AWMA-S)	STOPIT: response inhibition; AWMA: working memory	Improvement in working memory but not in response inhibition post-intervention vs pre-intervention
Shema-Shiratzky	2018	Single group-pilot study	No	14 (11 male, 3 female)	9.3+/-1.2	ADHD	Other (walking)	Low	6 week duration (3 sessions ranging from 30 min- 1 hr per week)	Stroop Test, Go-NoGO Task, color trails test	Stroop and : response inhibition; CTT: attention/ set shifting and response inhibition	Improvement in attention /set shifting and response inhibition post-intervention vs pre-intervention
Ringenbach	2015	Crossover study	Not reported	10	12.3+/-2.2	ASD	Cycling	Low	20 minute session	Stroop Task, Trail Making Test	ST: Inhibition; TMT: attention/set shifting	All three improved significantly post-intervention vs pre-intervention

Study			Sample characteristics				Intervention			Findings		
Author	Pub Year	Study design	Co-morbid stimulant medication	Sample Size	Age range (M+\- SD)	Diagnosis	Type	Intensity	Duration	EF Measure	EF Domain	Key Result
Ludyga	2017	Crossover study	Yes	16 (11 male, 5 female)	12.8+/-1.8	ADHD	Cycling	Moderate-high intensity	20 min session	Flanker Test	Attention/set shifting	Greater improvement in reaction time not accuracy in exercise group compared to control group
Lee	2017	Parallel group	No	12 (all males)	8.83 +/-0.98	ADHD	Mixed (jumprope, jogging, etc)	Moderate-high intensity	12 week duration (3 60 minute sessions per week)	Stroop Color and word test	Response inhibition	Improvement in inhibition in exercise group post-intervention vs pre-intervention
Piepmeier	2015	Parallel group	Yes	14 (five females, 9 males)	10.14+/-1.96	ADHD	Cycling	Moderate-high intensity	20 minute session	Trail Making Test, Stroop	TMT: attention/set shifting; Stroop: response inhibition	Improvement in inhibition, not in attention/set shifting in exercise group compared to controls.
Chuang	2015	Crossover study	No	19 (16 males, 3 females)	9.42+/-1.38	ADHD	Running	Moderate-high intensity	30 minute session	Go/No go Task	Response inhibition	Greater improvement in attention/set shifting and response inhibition in exercise group compared to controls
Pan	2017	Crossover wait-list control study	Not reported	22 (all males)	age 6-12	ASD	Other (table tennis)	Unreported	12 week duration (2 70 min sessions per week)	Wisconsin card sorting test (WCST)	Attention/set shifting	Greater improvement in total correct, perseverative response, and conceptual -level response subscores of WCST after exercise
Ringenbach	2015	Crossover study	Not reported	10 (5 male, 5 female)	12.3+/-2.2	ASD	Cycling	Low	20 minute session	Stroop Task, Trail Making Test	ST: Inhibition; TMT: attention/set shifting	Greater improvements in exercise group compared to controls

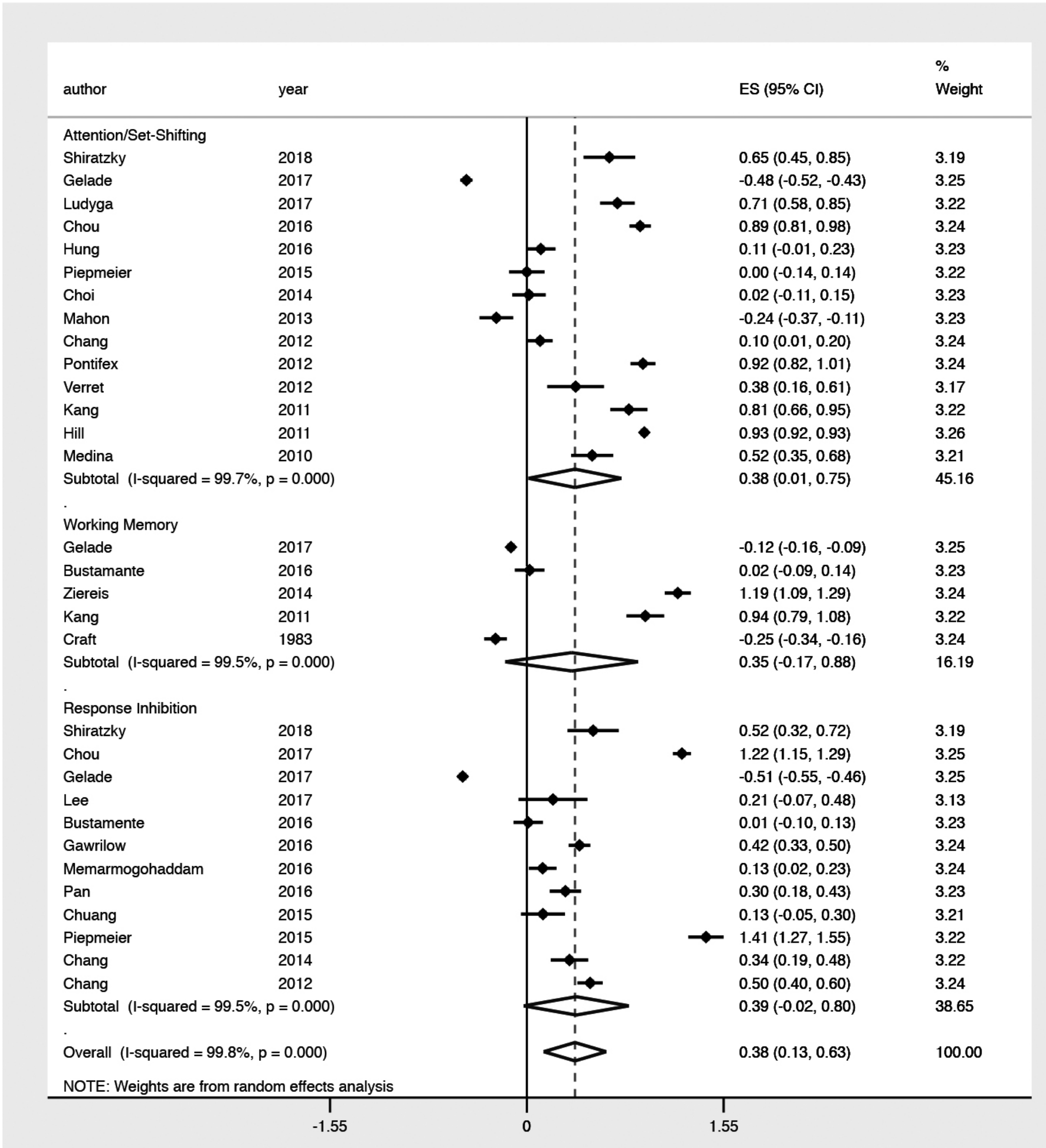

Figure 2.

ASD/FASD and exercise

Five studies conducted exercise interventions for children with ASD/FASD (total N of participants was 84). Studies were small: the sample size of persons with ASD/FASD ranged from 10[56] to 30[23]. All studies used a within-subjects randomized crossover design, with the exception one study[57] which used an A-B sequential design (control then intervention). No studies included a healthy control group. Exercise interventions varied in terms of frequency, intensity, and type of exercise. Detailed characteristics on the included studies are presented in Table 1.

Attention and set-shifting

The overall pooled ES was 0.69 (95% CI -0.28-1.66, k = 4) (Figure 3). The I^2 test of heterogeneity was statistically significant ($I^2 = 98.5\%$, df = 3, $p < 0.01$). Meta-regressions of sample size N, mean age of study participants, and year of study publication on ES were not significant. Begg's and Egger's tests did not demonstrate evidence of publication bias.

Working memory

Only two pilot studies (reporting data from 22 children) investigated the relationship between exercise interventions and working memory (Anderson-Hanley, 2011). Both studies reported a significant improvement of working memory following exercise intervention, using an A-B sequential control design. The overall pooled ES was 1.36 (95% CI 1.08-1.64, k = 2).

Response inhibition

The overall pooled ES was 0.78 (95% CI 0.21-1.35, k = 4) (Figure 3). The I^2 test of heterogeneity was statistically significant ($I^2 = 92.7\%$, df = 3, $p < 0.01$). Meta-regressions of sample size N, mean age of

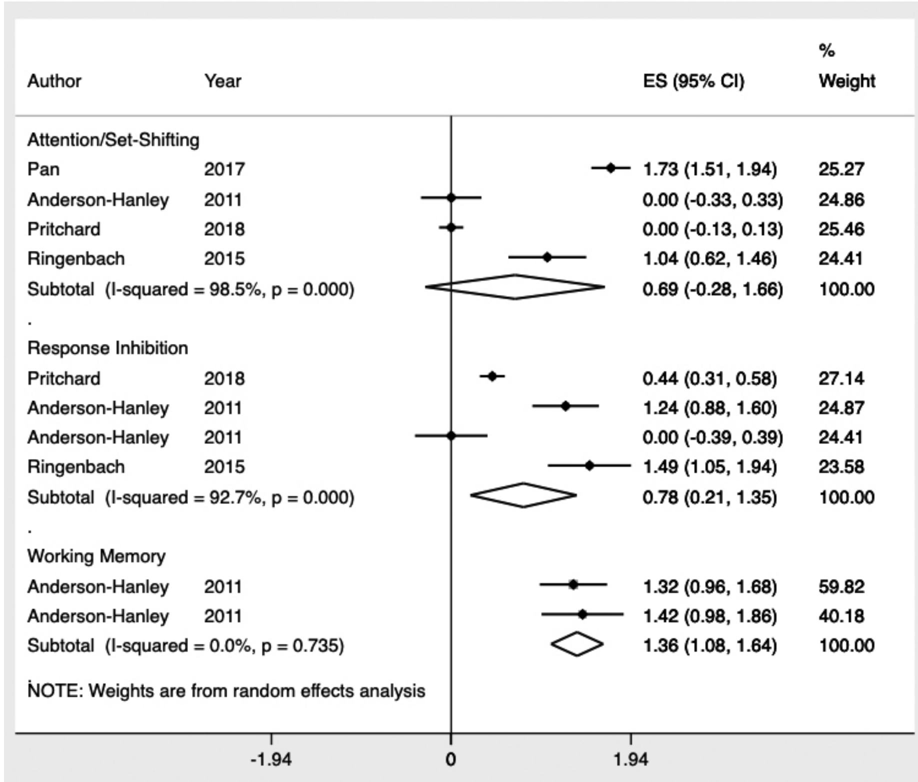

Figure 3.

study participants, and year of study publication on ES were not significant. Begg's and Egger's tests did not demonstrate evidence of publication bias.

Discussion

Exercise interventions among children and adolescents with neurodevelopmental disorders were associated with moderate improvements in executive function domains. Of note, studies of youth with ASD and FASD tended to report higher effect sizes compared to studies of youth with ADHD, albeit few existing studies. Exercise may be a potentially cost-effective and readily implementable intervention to improve executive function in these populations.

For ADHD, exercise interventions were associated with moderate improvements in attention/set-shifting and approached significance for working memory and response inhibition. Although this meta-analysis supports previous research[13,26] indicating exercise is associated with moderate improvements in EF in ADHD, it challenges a previous meta-analysis's findings that exercise has specific beneficial effects on response inhibition and working memory relative to attention or set shifting in children and adults with ADHD[24]. Nevertheless, it supports the notion that exercise may have specific beneficial effects in certain EF domains depending on the diagnosis. For ASD and FASD, exercise interventions were associated with large improvements in EF, notably response inhibition and working memory. This was a surprising result given the relative dearth of exercise intervention studies in ASD and FASD compared to ADHD. Sample size, mean age, study design, and the number or duration of intervention sessions did not significantly moderate the relationship between exercise and EF. Running interventions, compared to other forms of exercise, trended toward significance in moderating the effect of exercise on attention and set shifting in children and adolescents with ADHD. Only in the ADHD subgroup did stimulant medication use seem to moderate the relationship of exercise on improvement in response-inhibition but not in attention/set shifting or working memory.

Given the potential clinical implications of this meta-analysis, it is important to discuss the study's potential limitations. Heterogeneity in outcome measures made comparisons across studies difficult and resultant heterogeneity of ES estimates was high. As studies varied with regard to randomization and control of confounding variables, causal inferences must be limited. It also impeded attempts to explore predictors of better response to exercise. We sought to explore possible sources of heterogeneity using subgroup and meta-regression analyses. Results of meta-regressions should be interpreted with some caution due to the possibility of Type I errors, a known limitation of meta-regression[35]. Study bias was also evident in the existing literature, with a positive Egger's test for the association of exercise interventions and attention/set-shifting, wherein small studies tended to demonstrate larger effects than studies, suggesting that small negative studies are less likely to be published, and thus not included in the meta-analysis. Although exercise interventions were associated with large improvements in working memory in ASD and FASD (ES 1.36, 95% CI 1.08-1.64), conclusions are limited given the availability of only 2 studies.

Moving forward, studies using more standardized and robust methodologies, including larger sample sizes across a diverse range of comorbidities, are needed before recommendations can be made with regard to the dose, intensity, duration, and type of exercise. Further understanding of the effects of particular exercises on specific executive functioning domains (attention, set shifting, response inhibition, working memory) could be helpful in tailoring individualized exercise programs for children with different neurodevelopmental disorders. Research investigating the effect of co-morbid stimulant use to augment benefits of exercise in neurodevelopmental disorders is needed. Finally, research investigating the putative mechanisms for those improvements (i.e. BDNF or dopamine receptor upregulation) could be helpful in identifying additional treatments for children with executive functioning impairments.

Conclusions

Exercise interventions among children and adolescents with neurodevelopmental disorders are associated with moderate improvements in executive function, particularly in children and adolescents with ASD and FASD. Exercise may improve some EF domains more than others depending on the diagnosis. This meta-analysis finds that exercise has a moderate effect on EF in children and adolescents with ADHD and a large effect on EF in children and adolescents with FASD and ASD. There is a need to further investigate the relationship between exercise interventions and different domains of EF in children and adolescents with neurodevelopmental disorders, especially in ASD and FASD.

References

1. Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin--Allsopp M, et al., Trends in the prevalence of developmental disabilities in US children, 1997-2008. Pediatrics. 2011;127(6):1034-42.
2. Leitner Y. The co-occurrence of autism and attention deficit hyperactivity disorder in children – what do we know? Front Hum Neurosci. 2014;8:268.
3. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics. 2007;119(3):e733-41.
4. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 1997;121(1):65-94.
5. Kingdon D, Cardoso C, McGrath JJ. Research Review: Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder - a meta-analysis. J Child Psychol Psychiatry. 2016;57(2):116-31.
6. Childress AC, Sallee FR. Attention-deficit/hyperactivity disorder with inadequate response to stimulants: approaches to management. CNS Drugs. 2014;28(2):121-9.
7. Olfson M. New options in the pharmacological management of attention-deficit/hyperactivity disorder. Am J Manag Care. 2004;10(4 Suppl):S117-24.
8. Shim SH, Yoon HJ, Bak J, Hahn SW, Kim YK. Clinical and neurobiological factors in the management of treatment refractory attention-deficit hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2016;70:237-44.
9. Dougherty DM, Olvera RL, Acheson A, Hill-Kapturczak N, Ryan SR, Mathias CW. Acute effects of methylphenidate on impulsivity and attentional behavior among adolescents comorbid for ADHD and conduct disorder. J Adolesc. 2016;53:222-30.
10. Chronis AM, Jones HA, Raggi VL. Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. Clin Psychol Rev. 2006;26(4):486-502.
11. O'Connor MJ, Quattlebaum J, Castañeda M, Dipple KM. Alcohol Intervention for Adolescents with Fetal Alcohol Spectrum Disorders: Project Step Up, a Treatment Development Study. Alcohol Clin Exp Res. 2016;40(8):1744-51.
12. Chang YK, Labban JD, Gapin JI, Etnier JL. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res. 2012;1453:87-101.
13. Song M, Lauseng D, Lee S, Nordstrom M, Katch V. Enhanced Physical Activity Improves Selected Outcomes in Children With ADHD: Systematic Review. West J Nurs Res. 2016;38(9):1155-84.
14. Verburgh L, Königs M, Scherder EJ, Oosterlaan J. Physical exercise and executive functions in preadolescent children, adolescents and young adults: a meta-analysis. Br J Sports Med. 2014;48(12):973-9.
15. Ma Q. Beneficial effects of moderate voluntary physical exercise and its biological mechanisms on brain health. Neurosci Bull. 2008;24(4):265-70.
16. Meeusen R, De Meirleir K. Exercise and brain neurotransmission. Sports Med. 1995;20(3):160-88.
17. Wilens TE, Dodson W. A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. J Clin Psychiatry. 2004;65(10):1301-13.
18. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, et al. High impact running improves learning. Neurobiol Learn Mem. 2007;87(4):597-609.
19. Boehme F, Gil-Mohapel J, Cox A, Patten A, Giles E, Brocardo PS, et al. Voluntary exercise induces adult hippocampal neurogenesis and BDNF expression in a rodent model of fetal alcohol spectrum disorders. Eur J Neurosci. 2011;33(10):1799-811
20. Wigal SB, Emmerson N, Gehricke JG, Galassetti P. Exercise: applications to childhood ADHD. J Atten Disord. 2013;17(4):279-90.
21. Chang YK, Liu S, Yu HH, Lee YH. Effect of acute exercise on executive function in children with attention deficit hyperactivity disorder. Arch Clin Neuropsychol. 2012;27(2):225-37.
22. Cerrillo-Urbina AJ, García-Hermoso A, Sánchez-López M, Pardo--Guijarro MJ, Santos Gómez JL, Martínez-Vizcaíno V. The effects of physical exercise in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis of randomized control trials. Child Care Health Dev. 2015;41(6):779-88.
23. Pritchard Orr AB, Keiver K, Bertram CP, Clarren S. FAST Club: The Impact of a Physical Activity Intervention on Executive Function in Children With Fetal Alcohol Spectrum Disorder. Adapt Phys Activ Q. 2018;35(4):403-23.
24. Tan BW, Pooley JA, Speelman CP. A Meta-Analytic Review of the Efficacy of Physical Exercise Interventions on Cognition in Individuals with Autism Spectrum Disorder and ADHD. J Autism Dev Disord. 2016;46(9):3126-43.
25. Vysniauske, R., et al., The Effects of Physical Exercise on Functional Outcomes in the Treatment of ADHD: A Meta-Analysis. J Atten Disord, 2016.
26. Grassmann V, Alves MV, Santos-Galduróz RF, Galduróz JC. Possible Cognitive Benefits of Acute Physical Exercise in Children With ADHD. J Atten Disord. 2017;21(5):367-371.
27. Hoza B, Martin CP, Pirog A, Shoulberg EK. Using Physical Activity to Manage ADHD Symptoms: The State of the Evidence. Curr Psychiatry Rep. 2016;18(12):113.
28. Ash T, Bowling A, Davison K, Garcia J. Physical Activity Interventions for Children with Social, Emotional, and Behavioral Disabilities-A Systematic Review. J Dev Behav Pediatr. 2017;38(6):431-445.
29. Bremer E, Crozier M, Lloyd M. A systematic review of the behavioural outcomes following exercise interventions for children and youth with autism spectrum disorder. Autism. 2016;20(8):899-915.
30. Den Heijer AE, Groen Y, Tucha L, Fuermaier AB, Koerts J, Lange KW, et al. Sweat it out? The effects of physical exercise on cognition and behavior in children and adults with ADHD: a systematic literature review. J Neural Transm (Vienna). 2017;124(Suppl 1):3-26.
31. American College of Sports Medicine. ACSM's Exercise Testing and Prescription. Philadelphia: Lippincott Williams & Wilkins; 2000.
32. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9.
33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
34. Rosenthal R, Rosnow RL. Essentials of Behavioral Research: Methods and Data Analysis. 2nd ed. New York: McGraw-Hill; 1991.
35. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. Biostatistics. 2007;8(2):239-51.
36. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
37. Lee SK, Song J, Park JH. Effects of combination exercises on electroencephalography and frontal lobe executive function measures in children with ADHD: a pilot study. Biomed Res. 2017:S455-60.
38. Hill LJ, Williams JH, Aucott L, Thomson J, Mon-Williams M. How does exercise benefit performance on cognitive tests in primary-school pupils? Dev Med Child Neurol. 2011;53(7):630-5.
39. Geladé K, Bink M, Janssen TW, van Mourik R, Maras A, Oosterlaan J. An RCT into the effects of neurofeedback on neurocognitive functioning compared to stimulant medication and physical activity in children with ADHD. Eur Child Adolesc Psychiatry. 2017;26(4):457-68.
40. Kang KD, Choi JW, Kang SG, Han DH. Sports therapy for attention, cognitions and sociality. Int J Sports Med. 011;32(12):953-9.
41. Chou CC, Huang CJ. Effects of an 8-week yoga program on sustained attention and discrimination function in children with attention deficit hyperactivity disorder. PeerJ. 2017;5:e2883.
42. Choi JW, Han DH, Kang KD, Jung HY, Renshaw PF. Aerobic exercise and attention deficit hyperactivity disorder: brain research. Med Sci Sports Exerc. 2015;47(1):33-9.

43. Hung CL, Huang CJ, Tsai YJ, Chang YK, Hung TM. Neuroelectric and Behavioral Effects of Acute Exercise on Task Switching in Children with Attention-Deficit/Hyperactivity Disorder. Front Psychol. 2016;7:1589.
44. Verret C, Guay MC, Berthiaume C, Gardiner P, Béliveau L. A physical activity program improves behavior and cognitive functions in children with ADHD: an exploratory study. J Atten Disord. 2012;16(1):71-80.
45. Medina JA, Netto TL, Muszkat M, Medina AC, Botter D, Orbetelli R, et al. Exercise impact on sustained attention of ADHD children, methylphenidate effects. Atten Defic Hyperact Disord. 2010;2(1):49-58
46. Shema-Shiratzky S, Brozgol M, Cornejo-Thumm P, Geva-Dayan K, Rotstein M, Leitner Y, et al. Virtual reality training to enhance behavior and cognitive function among children with attention-deficit/hyperactivity disorder: brief report. Dev Neurorehabil. 2019;22(6):431-6.
47. Pontifex MB, Saliba BJ, Raine LB, Picchietti DL, Hillman CH. Exercise improves behavioral, neurocognitive, and scholastic performance in children with attention-deficit/hyperactivity disorder. J Pediatr. 2013;162(3):543-51.
48. Ludyga S, Brand S, Gerber M, Weber P, Brotzmann M, Habibifar F, et al. An event-related potential investigation of the acute effects of aerobic and coordinative exercise on inhibitory control in children with ADHD. Dev Cogn Neurosci. 2017;28:21-28.
49. Piepmeier AT. The effect of acute exercise on cognitive performance in children with and without ADHD. J Sport Health Sci. 2015;4(1):97-104.
50. Mahon AD, Dean RS, McIntosh DE, Marjerrison AD, Cole AS, Woodruff ME, et al. Acute Exercise Effects on Measures of Attention and Impulsivity in Children With Attention Deficit/Hyperactivity Disorder. J Educ Dev Psychol. 2013;3(2):65.
51. Bustamante EE, Davis CL, Frazier SL, Rusch D, Fogg LF, Atkins MS, et al. Randomized Controlled Trial of Exercise for ADHD and Disruptive Behavior Disorders. Med Sci Sports Exerc. 2016;48(7):1397-407.
52. Ziereis S, Jansen P. Effects of physical activity on executive function and motor performance in children with ADHD. Res Dev Disabil. 2015;38:181-91.
53. Craft DH. Effect of prior exercise on cognitive performance tasks by hyperactive and normal young boys. Percept Mot Skills. 1983;56(3):979-82.
54. Gawrilow C, Stadler G, Langguth N, Naumann A, Boeck A. Physical Activity, Affect, and Cognition in Children With Symptoms of ADHD. J Atten Disord. 2016;20(2):151-62.
55. Chuang LY. Effects of acute aerobic exercise on response preparation in a Go/No Go Task in children with ADHD: an ERP study. J Sport Health Sci. 2015;4:82-8.
56. Ringenbach SDR. Assisted Cycling Therapy (ACT) improves inhibition in adolescents with autism spectrum disorder J Intellect Dev Disabil. 2015;40(4):376-87.
57. Anderson-Hanley C, Tureck K, Schneiderman RL. Autism and exergaming: effects on repetitive behaviors and cognition. Psychol Res Behav Manag. 2011;4:129-37.

Supplemental Figure 1

Search Strategy
((autism) or (autism spectrum disorders) OR (adhd) OR (Attention Deficit Disorder with Hyperactivity) OR (attention-deficit hyperactivity disorder) OR (fetal alcohol exposure) OR (fetal alcohol spectrum disorders)) AND ((exercise) OR (physical activity) OR (physical fitness)) AND ((executive function tests) OR (executive function) OR (executive dysfunction) OR (Attention Capacity Test) OR (CANTAB) OR (COWAT) OR (CPT) OR (CCST) OR (D-KEFS) OR (IVA) OR (K-ABC) OR (NEPSY) OR (SOC) OR (SWM) OR (TEA-Ch) OR (TOVA) OR (TMT) OR (WCST) OR (WISC) OR (WMS) OR (WMTB-C))