Protection from genetic diathesis in ADHD: Possible complementary roles of exercise

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Abstract

Objective—The degree of functional impairment and adverse developmental outcomes in individuals with attention-deficit/hyperactivity disorder (ADHD) likely reflect interplay between genes and environment. To establish whether physical exercise might reduce the level of ADHD symptoms or ADHD-related impairments, we conducted a comprehensive review of the effect of exercise in children with ADHD. Findings on the impact of exercise in animals and typically developing humans, and an overview of putative mechanisms involved are also presented to provide the context in which to understand this review.

Method—The electronic databases PubMed, OVID and Web of Knowledge were searched for all studies investigating the effect of exercise in children and adolescents with ADHD, as well as animal models of ADHD behaviours (available in January 2013). Of 2,150 initially identified records, 16 were included.

Results—Animal studies indicate that exercise, especially early in development, may be beneficial for ADHD symptom reduction. The limited research investigating the effect of exercise in children and adolescents with ADHD suggests that exercise may improve executive functioning and behavioural symptoms associated with ADHD. While animal research suggests brain-derived neurotrophic factor (BDNF) and catecholamines (CAs) play a role in mediating these effects, the association between BDNF and ADHD remains unclear in humans.

Conclusions—The potential protective qualities of exercise with regard to reducing symptoms and impairments commonly associated may hold promise for the future. Further research is needed to firmly establish whether there are clinically significant effects of exercise on the severity of ADHD symptoms, impairments and associated developmental outcomes.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterised by developmentally inappropriate and impairing levels of hyperactivity, impulsivity and/or inattention.[1] ADHD is associated with multiple cognitive impairments, including lower average IQ[2], impairment in attentional processing, response inhibition and other aspects of executive functioning (EF)[3], which share genetic/familial risks with ADHD[3,4]. Genetic factors play a pivotal role in the susceptibility to ADHD, with 60-75% or more of the variance in ADHD symptoms attributable to genetic variation.[5,6] Environmental factors are also likely to contribute to the development of the disorder and associated emotional, behavioural and academic difficulties.[7] Moreover, the effects of genetic risks on development may depend on exposure to either adverse or enriched environments leading to

either negative or positive long term outcomes.[8,9] Such gene-environment interactions mean that specific environments may be more or less beneficial to the long term outcomes in children with ADHD.

Several environmental risk factors have been linked to ADHD.[7] Yet, less attention has been paid to *protective* factors that might reduce levels of ADHD symptoms and impairments associated with the disorder. We define protective factors as influences that increase adaptive functioning following environmental adversity or genetic risk. Here, we investigate exercise as a factor that may diminish an individual's level of ADHD symptoms or the impairments associated with the disorder by modifying the effects of genetic and environmental risks on developmental outcomes. We will investigate exercise as a factor that may diminish an individual's likelihood of developing ADHD or the impairments associated with the disorder. The idea that exercise may have protective qualities for individuals with ADHD gains support from animal research examining the impact of exercise on neural functioning, brain growth and development, as well as from human studies indicating that exercise positively affects executive functioning and inhibitory control in adults and typically developing children. Preliminary research has also been carried out to explore the utility of exercise as a protective factor or alternative treatment strategy in ADHD. Before providing a comprehensive review of the role of exercise in ADHD, we will provide the context in which to understand this review by presenting findings on the impact of exercise on cognition in animal and typically developing human research, and an overview of the putative mechanisms involved.

The neurobiology of ADHD

The precise neurobiological mechanisms underlying ADHD are poorly understood. Their complexity is likely due to the interplay of various structural, functional and developmental brain alterations in individuals with ADHD, such as abnormalities in the white matter fibres that connect grey matter regions, hypoactivity of frontal regions and aberrant or delayed brain development.[10] Dysregulation of dopaminergic and noradrenergic neurotransmission has also been widely implicated in the pathophysiology of ADHD.[11] The catecholaminergic system has been the key target for pharmacotherapy in ADHD.[12] In molecular genetic studies of ADHD, one of the most robust findings to date is the association with the 7-repeat allele of the dopamine D4 receptor gene[13], and the catecholamines (CA) are known to play a pivotal role in the regulation of psychomotor activity, motivation, inhibition, and attention[14], all of which are compromised in ADHD[12]. (For a comprehensive review of the neurobiology and genetics of ADHD, see [10,15]).

One recent theory has focused on BDNF as a factor that impacts on dopaminergic function underlying aspects of ADHD.[14,16-19] The idea that BDNF interacts with the dopaminergic dysfunctions seen in individuals with ADHD was initially suggested by research showing that stimulant medications increase the expression of BDNF in the rat brain[19], in addition to studies suggesting that there is an association between genetic variants in BDNF and risk for ADHD. In a community-based cohort of 1,236 Swedish individuals assessed at ages 8-9, 13-14 and 16-17 years, the presence of the Val[66]Met polymorphism in BDNF gene was

associated with increased hyperactive-impulsive ADHD symptom counts at ages 8-9 and 13-14 years.[19]

However, the overall evidence for the genetic association of BDNF with ADHD is far from clear. A recent meta-analysis of published and unpublished data from four different centres (conducted as part of the International Multicentre Persistent ADHD CollaboraTion; IMpACT) investigated the association of ADHD with the most frequently reported BDNF polymorphism, Val[66]Met, in a total sample 1,455 ADHD adults and 2,247 sex-matched controls.[20] The investigation of these four populations yielded no significant association between BDNF genotype and ADHD. Like several studies before[21-23], the investigation of these four populations yielded no significant association between BDNF and ADHD, highlighting the known difficulties in replicating candidate gene association studies; potentially related to heterogeneity of the genetic effects across development or related to different clinical subgroups.

The conception of exercise as a potential protective factor for ADHD is suggested by animal literature investigating the positive impacts of physical activity on neurobiological mechanisms implicated in ADHD. In healthy rodents, exercise has been found to augment several factors often compromised in ADHD: neural plasticity[24], cerebral blood flow[25], levels of synaptic protein[26] and extracellular dopamine and norepinephrine levels in the central nervous system[27]. Furthermore, physical exercise has been shown to lead to an increase in rodent serum and brain levels of BDNF, which is part of vital neurodevelopmental processes central to the survival and differentiation of noradrenergic[28] and dopaminergic[29] neurons.[30-34]

This upregulation of BDNF is one potential mechanism via which exercise induces its positive effects. BDNF levels in the hippocampus have been directly linked to the enhanced memory and learning processes that are observed with exercise treatments in rodents.[35] One process expected to mediate the upregulation of BDNF involves epigenetic influences on gene expression. Epigenetic processes, which developmentally regulate gene expression independently of the DNA sequence via modifications to DNA, histone proteins and chromatin[36], have been shown to be sensitive to a range of environmental influences[37]. Indeed, both acute[38] and chronic[39] exercise have recently been found to elicit gene expression changes linked to changes in DNA methylation. However, the strength of the association between BDNF and ADHD in humans and its potential role in eliciting the established positive effects of exercise on cognition and psychological health[40] remain unclear.

The cognitive effects of exercise in humans

Beyond the animal literature, an emerging body of evidence highlights the benefits of exercise for humans.[40] Research on the effect of exercise in humans has found, for example, that older adults, who were more aerobically fit or who took part in exercise programmes, demonstrated greater task-related activity in areas of the brain implicated in ADHD; namely regions of the prefrontal and parietal cortices, with the largest fitness-induced benefits occurring for executive functions.[41] Furthermore, there is evidence that in humans exercise facilitates catecholaminergic neurotransmission[42,43], augments serum BDNF levels[31,34],

enhances cognitive performance and affects cerebral structures positively by increasing cortical tissue density and brain volume[41,44]. A meta-analysis of 44 studies, which investigated the effects of both acute and chronic exercise on cognition in children, yielded an overall effect size (ES) of 0.32. Despite the ES being only moderate, these findings indicate a significant positive effect of exercise on cognitive performance. As the ES of exercise was greater in the children who were classified as "mentally impaired" (0.42), this moderate overall ES may point to greater beneficial effects of exercise in children with developmental disorders.[45] Other more recent reviews of the effects of exercise on neurotypical children's intelligence, cognition and academic achievement confirmed the positive effect of exercise, especially on EF[40,46,47], a cognitive domain often impaired in individuals with ADHD[48]. Chronic and acute exercise was reported to improve inhibitory control, while the effects on attention, perception and visuo-motor coordination were more limited.

The role of exercise in ADHD

Animal and neurotypical human studies, thus, provide support for the notion that exercise enhances brain structure, cognitive performance and neural functioning. As enhanced neural functioning has been suggested to be associated with a remission of ADHD symptoms[49,50], exercise may hold promise for preventing the emergence of ADHD during childhood, and as an early intervention in children presenting with high levels of ADHD symptoms, potentially inducing lasting changes in ADHD symptom severity. Our aim here, therefore, is to offer a review of the literature investigating the effect of exercise in ADHD, including cognitive impairments as well as ADHD symptoms, and to provide a rationale for further research in this area.

Selection criteria

A comprehensive review was conducted to ensure a thorough search of the literature. The electronic databases PubMed, OVID and Web of Knowledge were searched. Key words searched included *attention deficit hyperactivity disorder*, *ADHD*, *attention deficit disorder*, *ADD and hyperkinetic syndrome with either sport**, *exercise or physical activity*. The inclusion criteria for studies reviewed here were as follows: (a) written in English; (b) published in an internationally peer-reviewed journal before January 2013; (c) participants were children and/or adolescents diagnosed with ADHD or animal models of ADHD behaviours; (d) an empirical study (including correlational, observational and longitudinal designs) of aerobic exercise. Using these search terms and inclusion criteria, 2,150 records were identified. After screening these records for eligibility as shown in Figure 1, 16 studies were included in the comprehensive review. An overview of these studies can be found in Table 1.

The effects of exercise in animal models of ADHD behaviours

The impact of voluntary exercise on attentional functioning in spontaneously hypertensive rats (SHR), an animal model of ADHD behaviours, has been investigated in three studies by the same research group. The first and second study explored exercise effects in adult[51] and adolescent[52] SHRs, respectively. The third study compared the effects of exercise on adult

SHRs to the effects of the stimulant drugs methylphenidate (MPH) and atomoxetine (ATMX).[53] In all studies, the rats in the exercise groups had free access to a shared running wheel for a few weeks prior to and throughout the study. The exercise group was compared to other SHRs with no access to a running wheel (non-exercising SHRs). Wistar-Kyoto rats (WKY) were used as an animal model of neurotypical behaviours as they are the most appropriate controls for rat models of ADHD behaviours.[54] During the orienting procedure, all rats received repeated presentations of a visual stimulus (light). Hopkins et al.[51] showed that non-exercising adult SHRs demonstrated more unconditioned orienting behaviour, as indicated by rearing up on the hind legs, than WKY. Exercise reduced orienting in female but not male adult SHRs.

Exercising adolescent SHRs, similar to exercising female adult SHRs, exhibited levels of unconditioned orienting behaviour resembling WKY.[52] Non-exercising adolescent SHRs showed higher levels of unconditioned orienting behaviour. The authors propose that this indicates their difficulty ignoring irrelevant stimuli. Treatment with MPH (0.125 mg/kg), ATMX (0.125 mg/kg), or exercise also reduced orienting behaviour in female adult SHRs to the level observed in WKY rats, with exercise just as effective as MPH or ATMX. Taken together, these findings suggest that exercise has a greater effect in females and earlier on in development. Unfortunately, ES could not be established from the data available. These findings should be confirmed using quantifiable measures of exercise and a standardised measure of attention, such as a multiple-choice serial reaction time test.

The effects of involuntary exercise and MPH on activity levels and spatial learning memory in relation to dopamine synthesis and BDNF expression have also been explored in SHRs.[55] Rats in the MPH group received 1 mg/kg MPH orally once a day for 28 days, while rats in the exercise group were made to run on a treadmill for 30 minutes per day 5 times a week for 28 days. Both MPH and exercise alleviated hyperactivity effectively (see Table 1 for ES) and improved spatial learning memory; an effect seemingly mediated by the augmentation of dopamine levels and BDNF expression. These animal studies suggest that exercise could have a positive impact on symptoms of ADHD, especially early in development, potentially mediated by effects on BDNF and CAs.

The effects of exercise on individuals diagnosed with ADHD

While evidence for effects of exercise on symptoms and impairments associated with ADHD is limited, interest in novel treatment approaches is growing. It is, thus, encouraging that both chronic and acute exercise have been linked to improvements in EF in school-aged children with ADHD. One study investigating the effects of acute exercise on EF reported that 30 minutes of moderate-intensity running facilitated performance on the colour-word condition of the Stroop task and certain aspects of the Wisconsin Card Sorting Test in 20 children with ADHD randomly assigned to the exercise group, relative to 20 children with ADHD assigned to the control condition of watching an exercise-related video.[56] However, it should be noted that exercise did not have an effect on all measures of EF and that ES were small to moderate. Another study looking at the impact of acute exercise used a within-participant design to assess the effect of a 20-minute moderate-intensity bout of exercise in 20 children diagnosed with ADHD and 20 healthy-matched controls.[57] Following exercise,

both the ADHD and the control group exhibited greater response accuracy on a version of the Eriksen flanker task, measuring inhibitory control, relative to a seated reading condition. Acute exercise, thus, seems to have at least some effect on certain tasks assessing EF. The effect also seems to be universal and not specific to ADHD.

The impact of chronic exercise on EF has been assessed by measuring the amount of moderate- to high-intensity exercise performed by children with ADHD each day over a period of one week using an accelerometer.[58] Exercise quantity significantly predicted performance on the Tower of London task, and was positively associated with working memory, inhibition and information processing in 18 boys with ADHD. Similarly, a 6-week prospective trial of 12 bi-weekly sessions demonstrated that EF, as measured by the digit symbol test, was significantly improved by exercise relative to behavioural educational sessions in 28 boys with ADHD.[59] Teachers also noted significant improvements in the co-cooperativeness of boys in the exercise group, compared to boys who received behavioural education. While no significant changes were found with regards to hyperactivity scores, inattention scores improved in the exercise group.

A study examining the association between attention and chronic exercise in 84 individuals with ADHD employed a moderate-intensity 10-week exercise programme of three sessions per week, which included upper limb, lower limb, trunk and neck aerobic exercises, in addition to free running.[64] Individuals were randomly assigned to two equal groups: the exercise group and the control group which did not receive an exercise intervention.[60] In this study, exercise significantly improved teacher ratings of attention, motor skills and academic and classroom behaviour. Correspondingly, another study assessed the effects of a 10-week moderate-to-high-intensity exercise programme on fitness, cognitive functions and ADHD-related behaviour in 10 children with ADHD and compared the effects to a no-intervention control group consisting of 11 children with ADHD. This study reported significant improvements in muscular capacities, motor skills, level of information processing and parent- and teacher-rated social, thought and attention problems following the intervention.[61] The effect of chronic exercise on behaviour ratings was further investigated in a non-randomised 5-week exercise programme in 19 children with ADHD.[62] While no significant group differences were found between the exercise and no-exercise control group with regards to changes in parent-rated Conners' Rating Scale (CRS) scores, total behaviour, attention, emotional and motor skills were rated as having improved for both groups after the intervention. These findings suggest non-specific treatment effects, conceivably due to rater expectation, rather than real effects of exercise. This last view is consistent with a recent meta-analysis on non-pharmacological interventions for ADHD, which found that the ES for non-pharmacological interventions depended on the rater's blinding status.[63] While some studies of the effect of chronic exercise on EF used unblinded ratings and must be interpreted with caution, others are more convincing due to their use of relatively blinded raters, such as teachers and the objective cognitive tests they employed.

Another study focused on the association of exercise with different aspects of mental health seen in children with ADHD. In a retrospective study, participation in three or more sports was reported to be significantly associated with a reduced number of anxiety and depressive symptoms and rates of co-occurring mood disorders in children with ADHD compared to

control individuals with learning disabilities.[64] Yet, parent report of the number of sports a child plays is an arbitrary measure, as children playing one sport might be more dedicated to that sport and not necessarily less fit than children participating in more than one sport. As association does not imply causation, the correlation between the number of sports played and anxiety and depression symptoms could alternatively reflect that children who are less anxious are more likely to be engage in a greater number of different sports, or that depressed children have less need for social interaction and, thus, participate in fewer sports. However, a study exploring a sport-based group therapy programme in boys with ADHD and boys with other behavioural disorders supported the finding that sports participation (20 90-minute sessions over one school year) improves anxiety and other behavioural scores.[65] Yet, the intervention included group discussions as well as exercise, and it remains unclear how large the effect of each aspect of the intervention was on the outcome measure. Furthermore, the lack of a neurotypical control group does not allow for conclusions about specific effects of the intervention.

To elucidate the putative mechanism underlying the effects of exercise, three studies have investigated the relationship between CA levels and exercise in individuals with ADHD. Yet, findings are inconclusive and contradictory. Among the first to investigate the impact of exercise in individuals with ADHD, Tantillo et al.[66] studied the rate of spontaneous eye blinks (SEB), the acoustic startle eye blink response (ASER) and motor impersistence, as non-invasive measures sensitive to dopamine agonists, in 8- to12-year-olds with and without ADHD. Although SEB and ASER had previously been used as sensitive measures of dopamine function in children with ADHD[67,68], no clear link between ASER and ADHD has been established in humans. Both the ADHD and control group underwent two bouts of exercise and one rest condition on consecutive days. The main findings were increased SEB rate, decreased latency of ASER and improved motor persistence following exercise in boys with ADHD, whereas such improvements were not observed in controls. Although the authors concluded that exercise augments dopamine levels in children with ADHD but not in neurotypical controls, the alternative interpretation is that the physiological effect is consistent across groups but emerges as significant only in those showing pathological levels of ADHD symptoms. In a more direct investigation of CA levels in response to exercise, Wigal et al.[69] compared ten children with combined subtype ADHD, to eight age and gender matched controls on their CA levels following two separate cycling ergometer sessions. CA levels were measured by a radio-enzymatic technique based on the conversion of the CA to radiolabeled metanephrine and normetanephrine. This CA assay uses an extraction technique that eliminates substances that may inhibit the radio-enzymatic assay and concentrates the CA to provide a more sensitive assay. Although epinephrine and norepinephrine levels rose in both groups following the exercise sessions, the response was less strong in children with ADHD and, in contrast to controls, their dopamine levels did not increase significantly, contrary to the previous study. The most recent study that examined the relationship between high-intensity exercise, CA levels and sustained attention in 25 children with ADHD demonstrated that exercise significantly improved response time and normalised impulsivity and vigilance measures, independent of CA.[70] Participants, who were divided into stimulant medication users and non-users, were assessed on Conners' Continuous Performance Test-II (CPT) at diagnosis, after exercise, and after a 1-minute

stretching session (control measure). As chronic use of MPH was associated with significant physiological and attentional effects, a comparison of stimulant users and non-users on CPT performance suggested that the improvements in cognition seen following exercise were not CA dependent. Yet, CA levels were not measured directly and no straightforward conclusion can be drawn from these findings. Furthermore, practice effects may be expected since the CPT was repeated after only a 1-minute stretching session. Although these findings must be approached cautiously due to these and other crucial study design limitations outlined below, the research investigating the effect of exercise on ADHD provides preliminary evidence of the potential for exercise to reduce emotional, behavioural and neuropsychological problems seen in children with ADHD.

Overall, based on the limited body of research conducted to date, we can conclude that exercise emerges as a potentially promising intervention for improving EF and behavioural symptoms associated with ADHD. Yet, many of the findings remain inconclusive and warrant further investigation. ES varied from small for auditory sustained attention[61] to large for response accuracy[57] (see Table 1). Conflicting findings have also been presented for the putative mechanism involved. This may be explained by several limitations. Concluding causality from non-randomized, retrospective and cross-sectional data is problematic. Not all of the studies reviewed here are case-control studies and those that do look at case-control differences are limited by small sample sizes and inadequate control conditions. The unblind status of the researchers and scorers may further inflate the positive effects of exercise on the various outcome variables due to the non-specific effects evoked by a child's participation in a treatment programme. Finally, the heterogeneous nature of and various treatment approaches to ADHD are seldom taken account, complicating the interpretation and generalisability of the results.

Conclusion

ADHD is best considered in a developmental framework. One neurodevelopmental model of ADHD views the disorder as resulting from early aberrations in brain development which remain relatively static throughout an individual's life time.[71] Yet, the plasticity of the brain and its interconnected neural circuits allow for recovery from ADHD symptoms and associated impairments over the course of development. Thus, experience-dependent neurodevelopmental processes, such as synaptic pruning or myelination, if facilitated early in childhood, could be used to aid the recovery from ADHD symptoms or mitigate symptomatic escalation over development. As exercise has been found to enhance neural growth and development, and improve cognitive and behavioural functioning in neurotypical individuals and animal studies, we reviewed the literature on the effects of exercise in children and adolescents with ADHD and animal models of ADHD behaviours.

A limited number of undersized non-randomized, retrospective and cross-sectional studies have investigated the impact of exercise on ADHD and the emotional, behavioural and neuropsychological problems associated with the disorder. The findings from these studies provide some support for the notion that exercise has the potential to act as a protective factor for ADHD. Further, better-quality evidence is however needed, to firmly establish the nature and extent of positive effects of exercise on children with ADHD. Researchers will

need to examine both acute and chronic effects of exercise in large, adequately powered, blind sham-controlled randomised clinical trials. In addition, follow-up studies are needed to establish whether any short-term effects are followed by longer term benefits of both acute and chronic exercise. Although it remains unclear which role, if any, BDNF plays in the pathophysiology of ADHD, enhanced neural functioning has been suggested to be associated with the reduction of remission of ADHD symptoms.[49,50,72] As exercise can elicit gene expression changes mediated by alterations in DNA methylation[38], the possibility emerges that some of the positive effects of exercise could be caused by epigenetic mechanisms, which may set off a cascade of processes instigated by altered gene expression that could ultimately link to a change in brain function.

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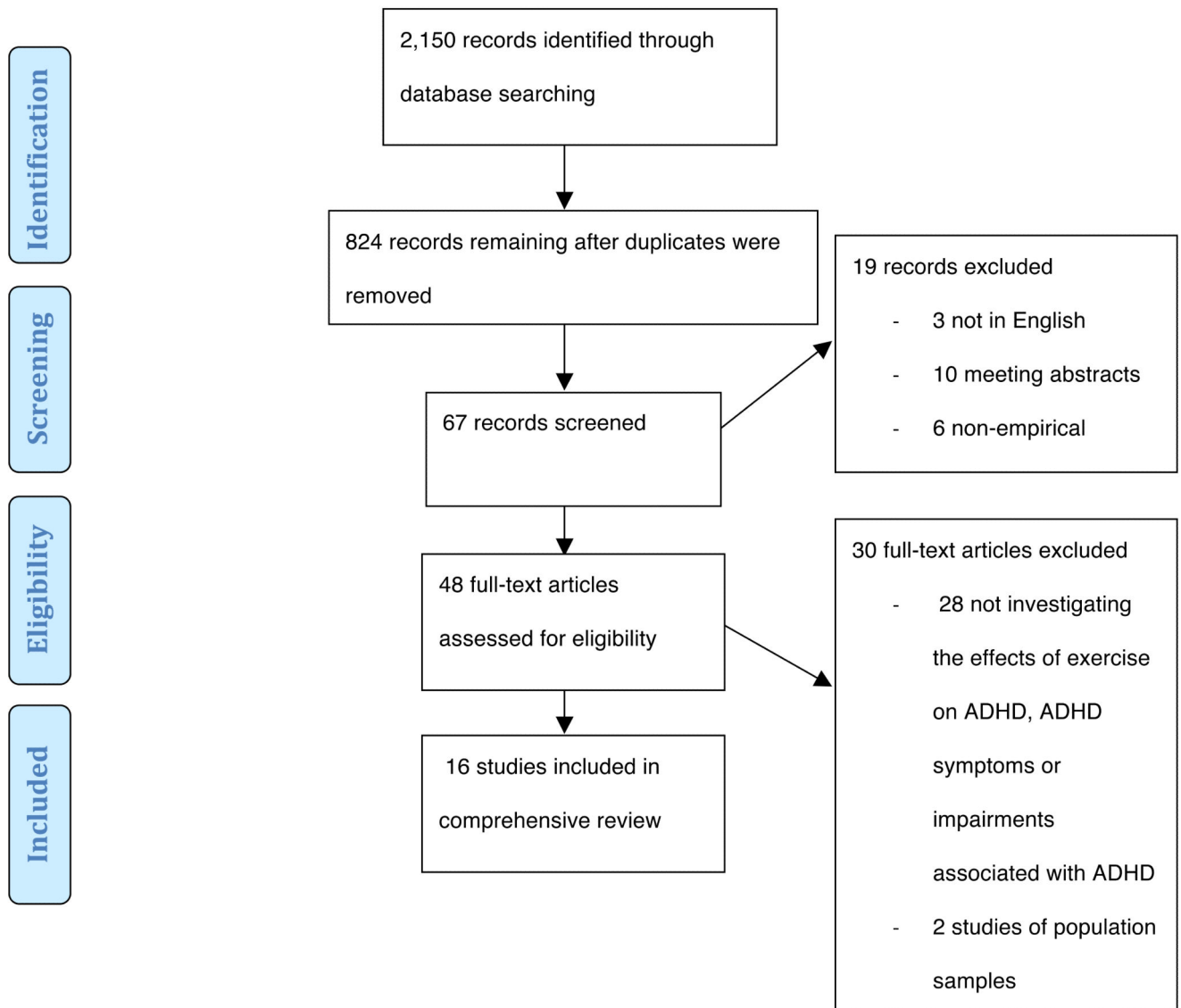
Figure 1.
Flow diagram depicting the number of records identified, included and excluded in the comprehensive review, and the reasons for exclusions. Source: Moher et al. (2009)[73].
ADHD= attention-deficit/hyperactivity disorder.

Table 1

Overview of all the studies on exercise and attention-deficit/hyperactivity disorder (ADHD) included in the comprehensive review. CBCL= Child Behaviour Checklist; CRS= Conners' Rating Scale; EF= executive function; ES= effect size; SHR= spontaneously hypertensive rat; MPH= methylphenidate; WCST= Wisconsin Card Sorting Test; WKY = Wistar-Kyoto rat

Sample type	Citation	Design	Intervention/ Measure of physical activity	Sample size (males: females)	Mean age (SD) in years unless stated	Cohen's d
Animal literature	Hopkins et al. (2009)[51]	Case-control (three-groups)	*SHR exercise group*: 24h access to running wheel, 2 weeks prior to and throughout study SHR no-exercise group: no intervention *WKY group*: no intervention	69 SHRs (37:32), 29 WKYs (14:15)	8 weeks	Orienting behaviour; data not available
	Kim et al. (2011)[55]	Case-control	*SHR exercise group*: low-intensity treadmill running 30 min/day, 5 times/week for 28 days *SHR MPH-treated group*: 1mg/kg MPH orally/day for 28 days SHR exercise and MPH-treated group SHR controls Controls	60 (60:0)	not available "adult"	Decrease in open field activity:2.85
	Robinson et al. (2011)[52]	Case-control	*SHR exercise group*: 24h access to running wheel, 3 weeks prior to and throughout study SHR non-exercise group: no intervention *WKY controls*: no intervention	32 SHRs (16:16), 16 WKYs (8:8)	28-32 days	Orienting behaviour; data not available
	Robinson et al. (2012)[53]	Case-control	*SHR exercise group*: 24hr access to running wheel, 3 weeks prior to and throughout study, saline-injection *SHR controls*: saline-injection *SHR MPH-treated group*: 1.0ml/kg 10min before behavioural task *SHR atomoxetine-treated group*: 1.0ml/kg 30min before behavioural task WKY controls WKY exercise group WKY MPH-treated group WKY atomoxetine-treated group	74 SHRs (0:74), 32 WKYs (0:32)	8–9 weeks	Orienting behaviour; data not available
ADHD	Ahmed and Mohamed (2011)[60]	Case-control, randomly assigned	*Exercise group*: 3 sessions/week for 10 weeks (aerobic exercise)	84 (54:30)	13.9 (1.6)	Attention:0.50 Motor skills:0.59

Sample type	Citation	Design	Intervention/ Measure of physical activity	Sample size (males: females)	Mean age (SD) in years unless stated	Cohen's d
			Controls: no intervention			Academic and classroom behaviour: 1.1
	Chang et al. (2012)[56]	Case-control, randomly assigned	*Exercise group*: acute moderate-intensity exercise (30min) *Controls*: watched exercise-related video (30min)	40 (37:3)	10.4 (0.9)	Colour-Word Stroop:0.57 Total WCST:0.31
	Gapin et al. (2010)[58]	Within-group comparison	Daily step counts and minutes/day spent in moderate-to-vigorous intensity exercise over 7 days	18 (18:0)	10.6 (1.5)	Tower of London task: 0.57
	Kang et al. (2011)[59]	Case-control	*Exercise group*: medication and sports therapy (12 90-min sessions over 6 weeks) *Controls*: medication and behaviour control education	28 (28:0)	8.5 (1.2)	Attention ratings:0.32 EF:0.37 Cooperativeness:0.54
	Kiluk et al. (2009)[64]	Within-group comparison	CBCL indicating number of sport activities	65 (40:25)	Range: 6-14	Boys:1.52 Girls:1.23
	Lufi and Parish-Plass (2013)[65]	Clinical comparison	20 90-min sessions (including discussions, individual sport activity, team games)	32 (32:0)	10.9 (1.6)	Total CBCL:0.45
	McKune et al. (2003)[62]	Case-control, allocation to groups	*Exercise group*: 5 1-h sessions/week for 5 weeks *Controls:* no intervention	19 (13:6)	11 (1.9)	CRS-Parent; data not available
	Medina et al. (2010)[70]	Between-group (MPH users v. non-users) comparison	30min aerobic exercise	25 (25:0)	9.5 (2.9)	Hit RT SD:0.49
	Pontifex et al. (2012)[57]	Case (ADHD) – control (neurotypical) and within-group comparison	Acute 20min moderate-intensity aerobic exercise	40 (28:12)	9.6 (0.5)	Response accuracy:0.94
	Tantillo et al. (2002)[66]	Case-control	Two exercise bouts (1st max. intensity, 2nd submax. intensity), one rest condition (silent cartoon); on consecutive days	43 (21:22)	10 (1.6)	Acoustic startle-eye-blink response latency: 1.14
	Verret et al. (2012)[61]	Case-control	*Exercise group*: 3 45-min sessions/week for 10weeks (moderate-to-vigorous aerobic, muscular and motor-skills exercise) *Controls*: no intervention	21 (20:1)	9.1 (1.1)	Attention problems: 1.68 Auditory sustained attention:0.13
	Wigal et al. 2003[69]	Case-control	Two separate cycle ergometer sessions on different days within a week	18 (18:0)	8.5 (0.5)	Catecholamine response; data not available