Is physical activity causally associated with symptoms of attention-deficit/ hyperactivity disorder?

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Abstract

Objective. Emerging evidence suggests that physical activity (PA) enhances cognition and may be a protective factor for attention-deficit/ hyperactivity disorder (ADHD). Yet, the impact of PA on ADHD symptoms has only been investigated in a few undersized, non-randomised and retrospective studies. We examined the effect of PA during late adolescence on ADHD symptoms in early adulthood while controlling for unmeasured genetic and shared environmental confounding. Methods. The effect of PA at age 16-17 (baseline) on ADHD symptoms at age 19-20 (follow-up) was examined using a within-monozygotic twins fixed-effects model in 232 monozygotic twin pairs born in Sweden between May 1985 and December 1986. Parents rated their children’s DSM ADHD symptoms at baseline and follow-up. Participants’ weekly energy expenditure (in metabolic equivalent task minutes/ week) was based on self-reports at baseline of PA frequency, intensity and duration. Results. Greater weekly energy expenditure in adolescence was significantly associated with reduced ADHD symptom levels in early adulthood, even when controlling for unmeasured confounding (all genetic and shared environmental factors shared within MZ twin pairs) and ADHD symptoms and BMI at baseline, β = -0.21, p=0.013 (95% CI= -0.38 – -0.05). Similar results were observed for the two ADHD sub-components; hyperactivity/ impulsivity, β = -0.21, p=0.022 (95% CI= -0.39 – -0.03), and inattention, β = -0.19, p=0.049 (95% CI= -0.36 – -0.0005). Conclusion. In line with a causal hypothesis, PA was inversely associated with ADHD symptoms, even after adjusting for unmeasured confounding. These findings suggest that PA in adolescence might decrease ADHD symptoms in early adulthood. However, given the size of the effect, the clinical value of this intervention needs to be explored further.
Introduction

Attention-deficit/ hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterised by developmentally inappropriate and impairing levels of hyperactivity, impulsivity, and/or inattention. Both the symptoms and functional impairments associated with ADHD persist from childhood into adolescence and adulthood in around 65% of cases. Across the lifespan, ADHD is associated with a significant risk of lower academic and occupational achievement, interpersonal problems, mental illness, and delinquency. Multimodal treatment plans including psychostimulant medication, non-psychostimulant medication and psychological interventions, tailored to the specific needs of the patient, are recommended for the treatment of ADHD. Due to their persistence, there is a continued need for treatment and management of ADHD symptoms and impairments from childhood through adolescence and into adulthood.

A robust evidence base stemming from randomised control trials attests to the efficacy of psychostimulant and non-psychostimulant medication in reducing the symptoms of ADHD. Yet, treatment with medication has its limitations. Some individuals may not respond to medication and complete normalisation of symptoms is rare. Medication may be less effective for treating associated impairments of ADHD, such as poor social skills and executive function (EF) deficits; and its long-term effectiveness for control of ADHD symptoms and impairments is yet to be established. Adverse side effects on sleep, appetite, and growth are also possible. Furthermore, some patients, parents and clinicians have reservations about medication use and the majority of individuals who are prescribed medication stop taking it within the first year. These potential problems are acknowledged by the National Institute for Health and Care Excellence (NICE) clinical guidelines which recommend that non-medical interventions should be considered as possible first line treatment where ADHD is associated with moderate levels of impairment.

A variety of non-pharmacological interventions, such as psychological (cognitive training, neurofeedback, and behavioural training) and dietary (restricted elimination diets, artificial food colour exclusions, and free fatty acid supplementation) interventions, are also available. A recent meta-analysis found blinded evidence that behavioural interventions used to treat children and adolescents
with ADHD had beneficial effects on important aspects of child and parent functioning, namely decreasing comorbid childhood conduct problems and increasing positive parenting\textsuperscript{14}. Yet, the evidence for the efficacy of non-pharmacological treatment interventions on reducing ADHD symptoms is far from clear and limited by the unblind status of researchers and raters of behaviour as another recent meta-analysis by the same group concluded\textsuperscript{15}. Blinded evidence for small but significant reductions in ADHD symptoms was found only for free fatty acid supplementation and artificial food colour exclusion\textsuperscript{15}.

Identifying new non-pharmacological treatments on the basis of our growing understanding of the pathophysiology as well as risk and protective factors of ADHD would, therefore, be a significant advance in the management of ADHD. Animal research as well as studies of typically developing children, adolescents and adults suggest physical activity (PA) and exercise as a putative treatment target, potentially diminishing an individual’s level of ADHD symptoms and associated impairments\textsuperscript{16}. Here, PA is defined as any bodily movement, produced by skeletal muscles, that requires energy expenditure, while exercise is a subcategory of PA that is planned, structured, repetitive, and purposeful. Yet, more and better-quality evidence is needed to establish the impact of PA on ADHD symptoms and its efficacy in alleviating the symptoms and impairments associated with the disorder.

Findings from a study investigating the correlation between cognitions and exercise quantity are consistent with the notion that PA may be beneficial for individuals with high levels of ADHD symptoms and associated impairments. Exercise quantity was measured each day over a period of one week using an accelerometer in 18 boys diagnosed with ADHD. The study found that exercise quantity significantly correlated with working memory, inhibition and information processing\textsuperscript{17}. Yet, the correlational and non-randomised design prohibits causal interpretations and limits conclusions about efficacy.

A study assessing 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 compared to a no-intervention control group consisting of 11 children with ADHD reported significant improvements in
Three studies investigating the effect of PA in individuals with ADHD have employed a randomised prospective design. One of these studies examined the effects of acute exercise on EF\(^{19}\). Thirty minutes of moderate-intensity running facilitated selective attention, processing speed and set-shifting in 20 children with ADHD who were randomly assigned to the PA group, relative to 20 children with ADHD assigned to the control condition of watching a PA-related video\(^{19}\). The second study explored the association between chronic PA and attention in 84 children with ADHD. Compared to individuals who did not receive an intervention, individuals randomly assigned to a moderate-intensity 10-week exercise programme of three sessions per week improved on teacher ratings of attention, motor skills and academic and classroom behaviour\(^{20}\). In the third randomised study, teacher-rated cooperativeness and EF as indicated by the digit symbol test were significantly improved by 12 bi-weekly exercise sessions, relative to behavioural educational sessions, in 28 boys with ADHD\(^{21}\). While no significant changes were found with regards to hyperactivity scores, inattention scores improved in the exercise group. These randomised prospective studies, thus, suggest that PA has positive effects on EF and behavioural symptoms associated with ADHD. Yet, none of these studies established whether any short-term effects of PA were followed by longer-term benefits. Furthermore, none of these studies elaborate on the blinding status of the researchers and informants.

The findings from the studies reviewed above provide some support for the hypothesis that exercise has the potential to act as a protective factor for ADHD symptoms and associated impairments. Yet, concluding causality from non-randomised, retrospective, and cross-sectional data is problematic. The studies looking at case-control differences are also limited by inadequate control conditions and the results may, therefore, be confounded by unmeasured genetic and environmental factors that may lead to spurious associations. The non-blinded status of the researchers and raters of behaviour 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\(^{16}\). Furthermore, little is known...
about the developmental influence of PA on ADHD symptoms. The purpose of this study was to examine the effect of PA during late adolescence on ADHD symptoms in early adulthood. Both the symptoms and functional impairments associated with ADHD often persist from childhood into adolescence and adulthood. While attention problems remain relatively stable, symptoms of hyperactivity and impulsivity tend to decline with age. PA may, thus, be particularly beneficial for the age group examined here as PA seems to affect inattention more than hyperactivity/impulsivity symptoms. In the light of these findings, the impact of PA on ADHD symptoms is examined together and separately for the two sub-components of ADHD, inattention and hyperactivity/impulsivity. Investigating the effect in 232 monozygotic (MZ) twin pairs enables us to control for unmeasured genetic and shared environmental confounding factors that may influence the relationship between PA and ADHD symptoms, allowing us to draw tentative causal inferences about this relationship.

**Methods**

**Sample**

Data came from the Swedish Twin Study of Child and Adolescent Development (TCHAD). TCHAD is an on-going prospective longitudinal twin study concerning health and behaviour in twins from childhood to early adulthood. The study is a sub-sample of the Swedish Twin Registry, and contains about 1,450 twin pairs born in Sweden between May 1985 and December 1986. The twins and their parents have been contacted on four different occasions using postal questionnaires. The current study used data from waves 3 and 4. The TCHAD sample is representative of the Swedish population with regard to educational level and employment status, but not ethnicity. In wave 3, the response rate was 74 % for parents (n = 1,067), and 82 % for twins (n = 2,369). In wave 4, parents’ response rate was 40% (n =1,158) and the twin’s response rate was 59% (n = 1,705). The zygosity of 1312 twins was confirmed by DNA-test during wave 4 when all twins were asked to provide a DNA sample with the help of OraGenes DNA (DNA Genotek Inc., Ontario, Canada) self-collection kits. For 1,444 twins without a DNA sample, zygosity was determined based on an algorithm derived from discriminant analyses of twins’ and parents’ responses to validated questionnaires. In cases of any contradictions between the assignments (n=100, 3.4%), the zygodity was set to unknown, and the
twins were excluded from the analyses. The present study included 232 monozygotic (MZ) twin pairs who had completed self-report measures on PA at age 16-17 and whose parents had completed parent-report measures of ADHD symptoms at ages 16-17 and 19-20. The included MZ twins did not differ significantly from the individuals lost to follow-up with regards to physical activity levels (t= -0.53, df= 767, p= 0.60), ADHD symptoms in adolescence (t= -0.25, df= 839, p= 0.80) and ADHD symptoms in early adulthood (t= 0.69, df= 497, p= 0.49). 48.74% of the participants were male. Ethical approval was obtained from the Ethics Committee of the Karolinska Institute, Stockholm, Sweden. No informed consent was required because, according to Swedish rules, response to the questionnaire constitutes consent.

Measures

PA is defined as any bodily movement, produced by skeletal muscles, that requires energy expenditure. PA is a complex and multidimensional exposure and when assessing its effect, the intensity, duration, and frequency with which it is performed must be taken into account. The twins provided self-ratings of their PA by answering three multiple-choice questions enquiring about the intensity, frequency, and duration of their leisure-time PA (see Table 1). The intensity indicated by the participant was converted into metabolic equivalents of task (MET) using the Compendium of Physical Activities. The average duration per PA session indicated by the participant was converted into minutes/session respectively. PA frequency was converted into PA sessions/week. Weekly energy expenditure (EE) of PA was then calculated using the following formula:

\[
\text{Intensity (MET)} \times \text{Duration (min/time)} \times \text{Frequency (times/week)} = \text{weekly EE (MET-min/week)}
\]

Higher scores indicate greater PA.

At age 16-17, parents completed a binary-coded checklist (0= not true, 1=true) of 14 ADHD symptom items based on DSM-IV criteria. Because of the changes in DSM during the follow-up period of the TCHAD study, the full set of all 18 DSM-IV ADHD symptoms were not included. At age 19-20, parents provided ratings of their children’s ADHD symptoms based on the 18 DSM-IV items for ADHD via a Likert-type scale (0= not true; 1= sometimes true; 2=often true). At both time points, parents were asked to check symptoms persisting for at least 6 months. Separate scores for
inattention and hyperactivity-impulsivity as well as a total DSM-IV ADHD symptom score were established from these ratings. Higher scores indicate greater symptom severity.

Participants also provided their weight (in kilograms, kg), and height (in meters, m) at baseline. Each participant's body mass index (BMI) was calculated by dividing his/her body weight in kg by his/her height in m squared (kg/m²). Descriptive statistics for these variables can be found in Table 2.

Statistical analysis

The relationship between PA and ADHD symptoms was investigated using a within-MZ twins fixed-effect model\textsuperscript{30} which models within-MZ twin pair differences in ADHD symptoms as a function of within-pair differences of weekly EE. Thus, the analysis allows for the effect of PA on ADHD symptom levels to be estimated while accounting for unmeasured confounding factors (i.e. all genetic and shared environmental factors shared within MZ twin pairs). This is due to the fact that MZ twins share 100% of their inherited DNA sequence and are expected to share many aspects of their environment by virtue of being born at the same time and place and growing up in the same family. As ADHD symptoms and BMI\textsuperscript{31} at baseline were likely to be important confounders for the estimated effect of weekly EE on ADHD symptoms at follow-up, we included them in the model. Weekly EE and ADHD symptoms were studied as continuous variables. Models were fitted to standardised (Z-) weekly EE and ADHD symptom scores. Analyses were performed separately for inattentive, hyperactive/impulsive and total ADHD symptoms. All analyses were conducted in Stata 13.

Results

The within-MZ twins fixed-effect model revealed that greater weekly EE at age 16-17 significantly predicted reduced ADHD symptoms at age 19-20, $\beta = -0.30$, $p<0.001$ (95% CI= -0.46 – -0.15). Greater weekly EE at age 16-17 significantly predicted reduced ADHD symptoms at age 19-20 even when controlling for ADHD symptoms and BMI at baseline, $\beta = -0.21$, $p=0.013$ (95% CI= -0.38 – -0.05). Dimension-specific analyses indicated that, even when controlling for baseline BMI and hyperactivity/impulsivity and inattention symptom levels respectively, greater weekly EE at age 16-17...
was significantly associated with reduced hyperactivity/ impulsivity symptom levels at age 19-20, \( \beta = -0.21 \), \( p=0.022 \) (95% CI= -0.39 – -0.03), as well as with reduced inattention symptom levels at age 19-
20, \( \beta = -0.19 \), \( p=0.049 \) (95% CI= -0.36 – -0.0005). While the effect was slightly larger for hyperactivity/impulsivity symptoms, this difference was not significant, as indicated by the overlapping 95% confidence intervals. Because the analyses were carried out using standardised (Z-) scores, the beta coefficients presented in this section represent a standardised effect size measure such that one standard deviation change in EE leads to beta change in standard deviation in ADHD symptoms. The effect size is comparable to Cohen’s d.

**Discussion**

In the present study investigating the effect of PA on ADHD symptoms, higher levels of PA, indicated by higher weekly energy expenditure, in late adolescence was associated with lower ADHD symptom scores in early adulthood, even when adjusting for baseline ADHD symptoms, BMI and unmeasured genetic and shared environmental confounding factors. These results are in line with a causal hypothesis, indicating that PA may represent a protective factor for ADHD. By using a longitudinal design and focusing on weekly energy expenditure rather than a particular kind of exercise, we demonstrated that PA might have long-term beneficial effects on ADHD symptoms. These findings, therefore, strengthen and extend the limited body of research conducted to date which suggests that PA improves symptoms and impairments associated with ADHD\(^16\).

While previous research suggested a differential effect of PA on inattention and hyperactivity/impulsivity symptoms\(^ {18,20,21} \), we found that PA in late adolescence positively impacted on both inattention and hyperactivity/impulsivity symptom levels in early adulthood. Consequently, PA may offer benefits to individuals across development. As ADHD is often chronic, with prominent symptoms and impairment spanning from childhood into adolescence and adulthood\(^7\), these findings provide support for the idea that PA may represent a promising protective factor and novel treatment target for ADHD. The implementation of lifestyle changes in the form of more PA incorporated into daily routines, promoting an individual’s physical health, behaviour, and neuropsychological functioning, may have the potential for flattening the adverse trajectory of the disorder and yielding long-term
improvements. However, the effect of PA on ADHD symptoms is small to moderate (-0.21) in this population-based sample of twins and further research is needed to firmly establish the positive effect of PA and its magnitude in clinical populations. While the pathways via which PA may influence ADHD symptoms remain to be elucidated, the up-regulation of brain-derived neurotrophic factor (BDNF) is one potential mechanism by which PA could induce its positive effects on ADHD symptoms. However, the strength of the association between BDNF and ADHD in humans remain unclear\(^1\).

One limitation of this study lies in the use of continuous ADHD symptom ratings in a population-based sample rather than a focus on clinically diagnosed cases. Consequently, we cannot be certain that these findings will generalise to clinical populations of individuals diagnosed with ADHD and no firm conclusions about the clinical utility of PA on ADHD can yet be drawn. Furthermore, the analysis yielded a small to moderate effect size (-0.21) with uncertain impact on individuals with high levels of ADHD symptoms and impairments. However, the use of a large unselected sample may also be regarded as a strength because it decreases the risk of referral and selection biases associated with a clinical sample. Another limitation of this study is that we could not control for all factors that were not shared between the MZ twins and that may have influenced PA, ADHD symptoms or the association between PA and ADHD symptoms. Yet, we were able to adjust for all shared genetic and environmental factors by using fixed effects as well as for ADHD symptom levels and BMI at baseline (two potentially important unshared confounders of the association). The use of self-report to measure PA could be considered a limitation of our study\(^3\) because individuals with high levels of ADHD symptoms might report less accurately on PA due to difficulties with time estimation, EF and working memory. Yet, this issue is likely to be less pronounced in our unselected general population sample. Furthermore, our measure of ADHD symptoms has not been formally validated. Although we used cross-informant data (i.e., parent-report for ADHD, self-report for PA), relying on a single source of informant (e.g. lack of teacher report) to assess ADHD symptoms may be regarded as another limitation. However, DSM-based parent-rating scales have been shown to predict interview-based diagnoses in childhood and adulthood with adequate sensitivities and specificities\(^3\) and our ADHD instrument has been used in several epidemiological studies previously and has reproduced several well established findings in the ADHD literature\(^2\). Lastly, this study lacked a randomised
prospective design. Future randomised control trials will, therefore, have to substantiate the potential of PA to act as a protective factor for ADHD.

In line with a causal hypothesis, PA was inversely associated with total ADHD, hyperactivity/impulsivity and inattention symptoms, even after adjusting for unmeasured confounding factors, as well as ADHD symptom levels and BMI at baseline, indicating that PA may represent a protective factor for ADHD and a novel treatment target. Yet, research into the efficacy of PA as an intervention for ADHD is in its infancy. Methodologically robust, blinded, randomised controlled trials employing objective measures of PA are needed to investigate the effect of both acute and chronic PA on ADHD. In addition, prospective longitudinal studies are needed to establish whether any short-term effects are followed by longer-term benefits. In the future the intensity, frequency and duration of PA required to yield benefits for individuals with ADHD will need to be established. Whether PA lends itself to early intervention and prevention strategies also remains to be elucidated. Studies will need to affirm whether and to what extent factors such as age, fitness levels or ADHD symptom severity affect who is likely to respond to a PA-based intervention. It remains to be seen what the mechanisms are that underlie the positive effect of PA on ADHD symptoms and how far the effect extends beyond the core symptoms of ADHD.


Table 1. Physical activity questionnaire enquiring about the intensity, frequency, and duration of the participant's leisure-time physical activity.

<table>
<thead>
<tr>
<th>Question 1</th>
<th>How often do you exercise or play sports in your spare time?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answers 1</td>
<td>1. Never</td>
</tr>
<tr>
<td></td>
<td>2. Less than once a month</td>
</tr>
<tr>
<td></td>
<td>3. 1-2 times a month</td>
</tr>
<tr>
<td></td>
<td>4. About once a week</td>
</tr>
<tr>
<td></td>
<td>5. 2-3 times a week</td>
</tr>
<tr>
<td></td>
<td>6. 4-5 times a week</td>
</tr>
<tr>
<td></td>
<td>7. Almost every day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question 2</th>
<th>The intensity of your exercise is comparable to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answers 2</td>
<td>1. Walking</td>
</tr>
<tr>
<td></td>
<td>2. Walking/ jogging</td>
</tr>
<tr>
<td></td>
<td>3. Jogging</td>
</tr>
<tr>
<td></td>
<td>4. Running</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question 3</th>
<th>On average, how long are your exercise sessions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answers 3</td>
<td>1. Shorter than half an hour</td>
</tr>
<tr>
<td></td>
<td>2. Half an hour to under one hour</td>
</tr>
<tr>
<td></td>
<td>3. One hour to under two hours</td>
</tr>
<tr>
<td></td>
<td>4. Two hour or more</td>
</tr>
</tbody>
</table>
Table 2. Descriptive statistics for raw (non-standardised) scores.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly EE (MET-min/week) at age 16-17</td>
<td>44.47</td>
<td>30.46</td>
<td>0 – 153</td>
</tr>
<tr>
<td>Total ADHD symptoms at age 16-17</td>
<td>1.12</td>
<td>1.95</td>
<td>0 – 17</td>
</tr>
<tr>
<td>HI symptoms at age 16-17</td>
<td>0.32</td>
<td>0.88</td>
<td>0 – 9</td>
</tr>
<tr>
<td>IA symptoms at age 16-17</td>
<td>0.81</td>
<td>1.45</td>
<td>0 – 8</td>
</tr>
<tr>
<td>BMI at age 16-17</td>
<td>20.6</td>
<td>2.87</td>
<td>11.7 – 33.5</td>
</tr>
<tr>
<td>Total ADHD symptoms at age 19-20</td>
<td>2.50</td>
<td>3.48</td>
<td>0 – 28</td>
</tr>
<tr>
<td>HI symptoms at age 19-20</td>
<td>1.20</td>
<td>1.79</td>
<td>0 – 16</td>
</tr>
<tr>
<td>IA symptoms at age 19-20</td>
<td>1.30</td>
<td>2.18</td>
<td>0 – 18</td>
</tr>
</tbody>
</table>

SD = standard deviation; EE = energy expenditure; MET-min/week = metabolic equivalent of task minutes per week; ADHD = attention deficit hyperactivity disorder; HI = hyperactive/impulsive; IA = inattentive; BMI = body mass index