

Low cardiorespiratory fitness and obesity for ADHD in childhood and adolescence: A 6-year cohort study

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder in childhood and identifying risk factors associated with developing ADHD during childhood and adolescence is relevant from a clinical and epidemiological point of view.

Purpose: This work examines (1) whether overweight/obesity and low cardiorespiratory fitness (CRF) are associated with increased ADHD symptoms in childhood (cross-sectional analysis), and (2) whether overweight/obesity and low CRF levels during childhood predict increased ADHD symptoms in adolescence (longitudinal analysis).

Methods: Data were examined from a longitudinal study of Estonian inhabitants who took part in the European Youth Heart Study (EYHS) in 1998 and 1999 (baseline age 9 years), who were re-evaluated 6 years later as part of the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS). CRF was determined via an incremental maximal cycle-ergometer test, overweight/obesity was based on body mass index (BMI), and the 7-point of Klinteberg Hyperactivity Scale was used to assess ADHD symptoms at both time points.

Results: In the cross-sectional analysis, children with overweight/obesity were at greater risk of ADHD symptoms compared to underweight/normal-weight children, as were those unfit compared to fit children (OR=1.92 and 95%CI=1.02–3.55, and OR=1.84 and 95%CI=1.13–2.98, respectively). The cross-sectional association between BMI and ADHD symptoms was mediated by CRF ($z=2.116$, 42.9%; $p=0.034$). The longitudinal analysis showed being unfit in childhood was associated with a greater risk of increased ADHD symptoms 6 years later in adolescence (OR=2.26 and 95%CI=1.14–4.47), even after adjusting for baseline ADHD symptoms and BMI.

Conclusion: Our result suggests that being unfit is an additional risk factor for increased ADHD symptoms during childhood and adolescence. The association between BMI and ADHD symptoms was mediated by CRF in the cross-sectional analysis and no association was seen between overweight/obesity and increased ADHD symptoms.

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Keywords: body mass index, hyperactivity, aerobic fitness, youth, longitudinal study.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder that usually persists for the rest of a person's life.¹ It is linked to a developmental trajectory marked by the onset of comorbid disorders that likely increase the risk of mortality.^{2,3} These comorbid disorders, which include psychiatric problems such as oppositional defiant conduct, mood, anxiety, and substance use disorder,⁴⁻⁶ as well as somatic conditions such as obesity, diabetes mellitus, and hypertension,⁷⁻⁹ progress throughout childhood into adulthood and become major disease burden determinants.^{7,10,11}

The evidence linking ADHD with obesity is particularly robust.¹² Although longitudinal studies have shown ADHD in childhood to be a risk factor for obesity later in life,¹³⁻¹⁸ it is unclear whether obesity is also linked to ADHD on a mechanistic level.^{13,19,20} However, recent genetic evidence suggests that the molecular underpinning of ADHD and obesity may be shared.²¹ Particularly, a common neural substrate may (in part) underpin this shared genetic hypothesis.²²

Physical fitness is a set of attributes that determines a person's ability to perform physical activities that require cardiorespiratory fitness (CRF), endurance, strength, or flexibility. Specifically, CRF refers to the capacity of the circulatory and respiratory systems to supply oxygen to skeletal muscle for energy production needed during physical activity.²³ Physical fitness is strongly and negatively related to obesity.²⁴ Only a few studies, all exclusively cross-sectional and with relatively small sample sizes ($n < 198$), have examined the relationship between physical fitness and ADHD, with CRF the attribute most often studied.²⁵⁻³⁰ Jeoung³¹ found that Korean university students ($n=86$; age 22.60 ± 2.20 years) with low muscular strength and CRF were more likely to have increased ADHD symptoms than those of greater fitness. In contrast, Golubović, Milutinović, and Golubović³² found no differences in the physical fitness of pre-school children ($n=139$; age 6.3 ± 1.0 years) with and without a diagnosis of

ADHD. Over the last decade, neuroimaging studies have revealed positive associations between low CRF and impairments of cognitive function commonly involved in ADHD,^{33,34} and a recent study highlighted lower CRF to be associated with poorer interference control in Taiwanese children with ADHD.³⁵ Since lower CRF is related to poor cognitive functioning, and children with ADHD are more likely to have deficits in cognitive function, it might be hypothesized that lower CRF is also associated with increased ADHD symptoms. Due to the close link between CRF and body mass index (BMI), it may be that these two factors are inter-related in their association with ADHD, with one potentially mediated by the other, although this has not been investigated yet.

The present work examines (1) whether overweight/obesity and low CRF are associated with increased ADHD symptoms in childhood (cross-sectional analysis), and (2) whether overweight/obesity and low CRF during childhood predict increased ADHD symptoms in adolescence (longitudinal analysis). The possible mediation of the relationship between BMI and ADHD symptomatology by CRF, and the relationship between CRF and ADHD symptomatology by BMI, was also explored.

METHODS AND MATERIALS

Study sample and design

The study subjects were Estonian nationals who took part in the European Youth Heart Study (EYHS) in 1998 and 1999 (baseline age 9 years) who were re-evaluated 6 years later as part of the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS). The rationales and methods of these studies have been reported elsewhere.³⁶ Briefly, all schools in Tartu County (Estonia) were invited to participate. Of those that agreed (54 of a total 56), 25 schools were chosen at random, and schools from both urban and rural areas were enrolled. Of the 583 subjects initially enrolled in this

cohort study, 451 had valid data in all relevant variables included in the main analyses (gender, maternal education, CRF, BMI, and ADHD symptoms and were therefore included in the cross-sectional analyses. From those participants, 288 had valid data in these relevant variables both at baseline and follow-up 6 years later (i.e. at age 15 years), and were therefore used in the longitudinal analyses. No significant differences in the main study variables (i.e. CRF, BMI, or ADHD) were observed between included and excluded participants in both cross-sectional and longitudinal analyses. The study was approved by the Tartu University Ethics Review Committee on Human Research (no. 49/30-199). All subjects and their parents gave written informed consent to be included.

Determining overweight/obesity

Height (cm) and weight (kg) were measured following standard procedures. BMI (kg.m^2) was calculated and used as an indicator of overweight/obesity. Weight status was defined using the sex- and age-specific BMI cut-offs of the World Obesity Federation, and subjects categorized as underweight/normal weight or overweight/obese at the ages of 9 and 15 years.³⁷

Cardiorespiratory fitness

CRF was determined using an incremental maximal cycle-ergometer test. The work rate was preprogrammed on a computerized Monark 829E Ergomedic cycle ergometer (Monark Exercise, Vansbro, Sweden) to increase every third minute until exhaustion. Heart rate was registered continuously by telemetry using a Polar Sports Tester (Polar Electro, Kempele, Finland). The criteria for exhaustion was a heart rate of ≥ 185 beats/min and a subjective judgment made by the test leader that the subject could no longer keep up his/her efforts, even after vocal encouragement. The Hansen formula was used to estimate maximum oxygen consumption ($\text{VO}_{2\text{max}}$) in mL.min^{-1} : $12W + 5 \times \text{weight}$

(kg) (where W =power output calculated). BMI and VO_{2max} relative to bodyweight ($mL.kg^{-1}.min^{-1}$) were used in statistical models.³⁸ The sex-specific CRF cut-off points proposed in the meta-analysis of Ruiz et al.³⁹ were used to categorize participants as “Unfit” or “Fit” at the ages of 9 and 15 years.

ADHD symptoms

The 7-point of Klinteberg Hyperactivity Scale was used to assess ADHD symptoms;⁴⁰ assessments were made by the subjects' class teachers at both baseline and follow-up. This scale consists of three subscales: aggressiveness, concentration difficulties, and motor restlessness. Each subscale has seven response options (scored 1-7). The overall ADHD score was calculated by summing the concentration difficulties and motor restlessness subscales, and the subjects recorded as having low-moderate ADHD symptoms (score 1 to 8) or increased ADHD symptoms (score 9 to 14) at 9 and 15 years of age.

Potential confounders

Age, gender, and maternal education were deemed to be potential confounders. Maternal education was used to estimate socioeconomic status. Stepwise linear regression models were used to identify confounding variables to be controlled in the final analytical models (gender and maternal education were found to be related to ADHD symptoms and were included as covariates).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows v.23.0 (IBM Corp, Armonk, NY, USA). Significance was set at $\alpha=0.05$ for all analyses. Pearson correlations were used to examine the relationships between BMI and CRF. For the main analyses, the exposure terms

(BMI and CRF) were treated both in standardized z-score form (i.e., mean=0, standard deviation=1) and as dichotomous variables (using the cut-off points referred to above). Prior to the main analyses, we tested and observed differences in BMI ($P=0.055$), CRF ($P<0.001$), and ADHD ($P<0.001$) by gender (i.e. boys having higher values for the three variables than girls) and decide to adjust for gender in all the models. In addition, in the main analyses, we tested interactions by gender for BMI, CRF, and ADHD symptoms and we did not find any interaction, indicating that the associations are consistent. Therefore, we decide to present the data for the whole sample instead of split the results by gender.

Cross-sectional analysis: the relationship between BMI/CRF and increased ADHD symptoms in childhood

Logistic regression was used to calculate the odds ratio (OR) and confidence intervals (CIs) of having increased ADHD symptoms at 9 years of age depending on BMI and CRF. The dichotomous 'ADHD symptoms' variable at 9 years was entered as the dependent variable; the independent variables were BMI or CRF, entered as overweight/obesity or under/normal-weight and fit or unfit, respectively, at age 9 years. Two models were explored, with Model 1 controlling for gender and maternal education at age 9 years, and Model 2 controlling for the covariates included in Model 1 plus BMI or CRF at 9 years.

Longitudinal analysis: BMI and CRF in childhood as predictors of increased ADHD symptoms at adolescence

Logistic regression was used to examine the OR and CIs for increased ADHD symptoms at age 15 years according to CRF and BMI at 9 years of age. The same covariates used in the cross-sectional

analysis were used in the longitudinal analysis models, with an additional adjustment for ADHD at baseline in Model 1.

Mediation of the relationship between BMI and ADHD symptoms by CRF, and CRF and ADHD symptoms by BMI

Linear regression models were fitted by bootstrapping analysis using the Hayes' PROCESS macro for the above SPSS software to examine whether the cross-sectional association between BMI and ADHD symptoms was mediated by CRF (a resample procedure involving 10,000 bootstrap samples was used). This method assesses the direct effects (Equations 1, 2, and 3' in the Hayes' treatment) and total effects (Equation 3) described by the unstandardized regression coefficient and the significance of the relationship between the independent and dependent outcomes. Equation 1 regresses the mediator (CRF) against the independent variable (BMI). Equation 2 regresses the dependent variable (ADHD symptoms) against the independent variables. Equation 3 and Equation 3' regress the dependent variable against the mediator and the independent variable respectively. Indirect effects and 95% CIs were also included; mediation was deemed established if the indirect effect was significantly different to zero. Finally, the indirect effect was divided by its standard error, and a z test performed under the null hypothesis that the indirect effect is equal to zero (Sobel test). The percentage of the total effect accounted for by mediation using the unstandardized coefficient of Equation 1 x 3/2 was then calculated. The same procedure was followed to examine whether the cross-sectional association between CRF and ADHD symptoms was mediated by BMI and whether there were any similar types of mediation in the longitudinal models.

In further analyses, a negative binomial regression was performed to examine the associations between BMI, CRF, and ADHD symptoms using the variables in the continuous form (counts for ADHD symptoms).

RESULTS

Table 1 shows the characteristics of the study subjects. Increased ADHD symptoms were observed in 20.6% of subjects at baseline and 16.0% at follow-up. Some 13.5% of subjects were overweight or obese (1.5% were obese). Overweight/obesity increased by 1%, and low CRF by 14.2%, between childhood and adolescence. BMI and CRF at 9 years were inversely correlated ($r=-0.332$; $p<0.001$).

Cross-Sectional Analysis. Figure 1 shows the OR and 95%CI for increased ADHD symptoms depending on BMI and CRF at 9 years of age (panels A and B respectively) after controlling for sex and maternal education. Being overweight/obese was related to 92% higher odds of experiencing increased ADHD symptoms (OR=1.92, 95%CI=1.02–3.55), but this became non-significant after adjusting for CRF (OR=1.59 and 95%CI=0.82-3.09). Compared to fit children, unfit children had an 84% greater risk of having increased ADHD symptoms at 9 years (OR=1.84, 95%CI=1.13–2.98). This association was attenuated but remained significant after additional adjustment for BMI (OR=1.68, 95%CI=1.01-2.77).

Longitudinal Analysis. Figure 2 shows how BMI and CRF at 9 years are associated with increased ADHD symptoms at 15 years (panels A and B respectively). Unfit children had over twice the risk of increased ADHD symptoms 6 years later (OR=2.26, 95%CI=1.14–4.47) after adjustment for basic confounders, and even after additional adjustment for baseline BMI (OR=2.21, 95%CI=1.10-4.44).

Being overweight/obese in childhood was not significantly associated with ADHD symptoms in adolescence (OR=1.44, 95%CI=0.59-3.54).

Mediation Analysis. Figure 3 shows the cross-sectional mediation model for CRF in the association between BMI and ADHD symptoms. The relationship between BMI and ADHD was mediated by CRF, which accounted for 42.9% of the total effect ($z=2.116$, $p=0.034$). However, the relationship between CRF and ADHD was not mediated by BMI ($z=-0.899$, $p=0.369$; see Figure SM1 in supplementary material). Since overweight/obesity was not longitudinally associated with increased ADHD symptoms, the association could not be mediated by CRF, and indeed none was found in the longitudinal models (data not shown).

In further analyses analyzing ADHD symptoms as a continuous variable, all the significant associations described above for increased ADHD symptoms (dichotomous variable) disappeared, both in the cross-sectional and longitudinal models (see Tables SM1-SM2 in supplementary material). Figure SM2 (see in supplementary material) shows the highly skewed distribution of the ADHD symptom count both at 9 and 15 years.

DISCUSSION

This investigation into the association between overweight/obesity and CRF with ADHD symptoms in a population sample reports several novel findings. At baseline, unfit children were nearly twice as likely to have increased ADHD symptoms. Similarly, overweight/obese children were also at nearly twice the risk of developing increased ADHD symptoms. Effect sizes were slightly attenuated after adjusting for CRF and BMI. The cross-sectional analysis results suggest that CRF mediates the association between BMI and increased ADHD symptoms, but BMI does not mediate that between

CRF and ADHD symptoms. The longitudinal data showed that low CRF (i.e., being unfit) in childhood increased the probability of more than twice of having increased ADHD symptoms in adolescence (6 years later), independently of confounders and baseline BMI and ADHD levels (gender and maternal education). Being overweight/obese in childhood was not associated with ADHD in adolescence.

Interestingly, and in contrast to these findings, BMI and CRF were not associated with ADHD symptoms when analyzed as continuous variables. The discrepancy between the analyses involving dichotomous variables (which involved the use of cut-offs) and continuous variables (which did not) suggests that CRF and BMI are risk factors for more severe ADHD symptoms. Since ADHD is conceptually and clinically defined as an elevated number of ADHD symptoms, the present findings could be clinically important.

Overweight/obesity and ADHD

The present work is one of the very few longitudinal studies analyzing the relationship between overweight/obesity and having increased ADHD symptoms in childhood and adolescence (separated here by 6 years). There is a strong chance that the link between overweight/obesity and ADHD symptoms is bidirectional. Most previous studies have investigated whether ADHD increases the risk of future overweight/obesity. For example, Aguirre et al.¹⁵ found that childhood ADHD was associated with overweight/obesity during young adulthood in a female cohort, and Cortese et al.²⁰, in a 33-year follow-up study, found that male children with ADHD were at increased risk of overweight/obesity as adults.

The mechanisms underpinning the coexistence of these conditions are not completely understood. ADHD and overweight/obesity may share underlying features of genetic predisposition and/or

abnormalities in energy balance, etc.⁴¹ Circadian rhythm dysregulation has also been associated with ADHD in youth⁴² and with overweight/obesity at this time of life,⁴³ and may provide a link between ADHD and overweight/obesity.⁴⁴ Physical activity patterns are also a possibility;⁴¹ two studies note that obese children with ADHD also had low physical activity levels.⁴⁵ Low levels of physical activity could lead to childhood obesity, and, in turn, to increased ADHD symptoms.⁴¹ The work of our group, and that of others, implicates abnormalities in neural dopaminergic pathways in the link between ADHD and obesity.^{46,47}

In the present work, overweight/obesity in childhood did not predict increased ADHD symptoms 6 years later. This result might have been influenced by the low prevalence of obesity, but it does concur with the results of Khalife et al.¹⁷, who reported childhood overweight/obesity not to be a risk factor for increased ADHD symptoms 8 years later. In the present study, BMI was used as an indicator of overweight/obesity; although this anthropometric index is internationally used for this purpose, it should be remembered that it does not distinguish between fat and lean mass. However, Bowling et al.²⁰ found a fat mass at 6 years of age not to be associated with ADHD symptoms at 9 years of age, a result consistent with the findings of Khalife et al.¹⁷ and the present results.

CRF and ADHD

The present cross-sectional data suggest that low CRF may be a risk factor for increased ADHD symptoms. The ADHD-CRF relationship remained significant (though slightly attenuated) after adjustment for BMI, suggesting that increased ADHD symptoms, overweight/obesity, and low CRF during childhood might co-exist via several mechanisms. Certainly, CRF mediated the association between BMI and increased ADHD symptoms. Unlike overweight/obesity, the relationship between

CRF and ADHD has been little explored, but the present results are in line with those of the limited preliminary research performed in smaller-scale studies involving children.^{25,30}

Although the mechanisms underlying the association between CRF and ADHD are unknown, Ortega et al.⁴⁸ report relationships between CRF and the shape of the nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus in Spanish children, and a recent meta-analysis⁴⁹ found reductions in the volume of some of these regions in children with ADHD compared to non-ADHD controls. Thus, the differences in subcortical brain structures shared in ADHD and low CRF might have a common etiology. In addition, differences in brain structure depending on different levels of CRF in childhood have been consistently observed in recent investigations conducted by our group and others.^{50,51} It has also been suggested that increased ADHD symptoms may predispose to motor problems;⁵² in fact, neuroimaging studies have shown that common neurophysiological substrates may underlie both motor impairment and increased ADHD symptoms.^{53,54} Thus, structural brain variation might cause difficulties in fine and gross motor skills, which in turn could affect the correct execution of coordinated motor skills, impeding the ability to undertake physical activity and negatively influence CRF. Another possible link, given the widely documented comorbidity of ADHD and developmental coordination disorder (DCD),⁵⁵ may be reflected in the finding that youths with increased ADHD symptoms may have greater problems in developing certain motor skills and coordination patterns, leading to a low CRF.

Limitations

This study suffers from the limitation of a significant drop-out between baseline and follow-up, although no differences in the main predictor variables or outcomes were observed between those who were and were not lost to follow-up. In addition, the sample was from Estonia only, which may limit

the generalizability of the findings. Further, most of the overweight/obese subjects were overweight rather than obese - the prevalence of childhood obesity in Estonia is among the lowest in Europe.⁵⁶ The effect of obesity on ADHD symptoms might thus be larger in other cohorts with a higher prevalence of obesity. It should also be considered that the present analyses were not adjusted for psychosocial comorbidities such as anxiety and/or depression that might co-occur with ADHD symptoms. Finally, this study involved the identification of increased ADHD symptoms rather than relying on clinical diagnoses. However, prior work has shown that ADHD symptoms are a useful phenotype.^{21,57}

CONCLUSIONS

The present work helps confirm that overweight/obesity co-occurs with ADHD symptoms in childhood, but also shows it not to be a predictor of increased ADHD symptoms 6 years later. Importantly, low CRF was found to be a factor for increased ADHD symptoms, which may mediate the association between BMI and ADHD. Randomized-controlled trials are required to investigate whether improvements in CRF induced via exercise programs can reduce ADHD symptoms.

PERSPECTIVE PARAGRAPH

This is the first study to examine cross-sectional and longitudinal associations of overweight/obesity and CRF with ADHD symptoms in crucial transitional periods of life (childhood and adolescence). At the cross-sectional level, we show that overweight/obese and unfit children are nearly twice as likely to have increased ADHD symptoms as their normal weight and fit peers respectively. However, this association was not found in longitudinal analyses. In addition, our results suggest that CRF mediates the cross-sectional association observed between BMI and increased ADHD symptoms. The main

novelty and most important contribution of our study to existing knowledge is the finding that low CRF (i.e., being unfit) in childhood doubles the probability of having increased ADHD symptoms in adolescence (6 years later), independently of basic confounders, baseline BMI and baseline ADHD. The present study suggests that low CRF might be a novel risk factor for increased ADHD symptoms during childhood and adolescence. Additionally, our results suggest that the association between BMI and ADHD during childhood may be mediated by CRF. Future prospective studies are required to confirm or contrast these novel findings on CRF and ADHD symptoms, as are large randomized-controlled trials to investigate whether changes in CRF induced via exercise programs can reduce ADHD symptoms across different periods of life.

DECLARATION OF INTERESTS

None.

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LEGENDS FOR FIGURES

Figure 1. Cardiorespiratory fitness (CRF) and body mass index (BMI) as dichotomous variables (panels A and B) and the odds ratio of having increased ADHD symptoms at 9 years of age (cross-sectional analysis; n=451). OW/OB: overweight and obese; UW/NW: underweight and normal weight. All models were adjusted for gender and maternal education. The overall ADHD score was dichotomized: score 1-8 low-moderate ADHD symptoms, 9-14 increased ADHD symptoms (determined at age 9 and 15 years). The cardiorespiratory fitness cut-off points of Ruiz et al. (2016) and the BMI cut-off points of Cole & Lobstein (2012) were used to categorize subjects.

Figure 2. Cardiorespiratory fitness (CRF) and body mass index (BMI) as dichotomous variables at 9 years of age (panels A and B), and the odds ratio of having increased ADHD symptoms at 15 years of age (longitudinal analysis; n=288). OW/OB: overweight and obese; UW/NW: underweight and normal weight. All models were adjusted for gender and maternal education. The overall ADHD score was dichotomized: score 1-8 low-moderate ADHD symptoms, 9-14 increased ADHD symptoms (determined at age 9 and 15 years). The cardiorespiratory fitness cut-off points of Ruiz et al. (2016) and the BMI cut-off points of Cole & Lobstein (2012) were used to categorize subjects.

Figure 3. Cardiorespiratory fitness (CRF) as a possible mediator of the relationship between body mass index (BMI) and attention-deficit/hyperactivity disorder (ADHD) symptoms, adjusted for gender and maternal education. Cross-sectional analyses considering BMI as a dichotomous variable, CRF as a continuous variable, and ADHD symptoms as a continuous variable at 9 years of age.