What is the effect of ADHD stimulant medication on Heart Rate and Blood Pressure in a Community Sample of Children?

Abbreviated Title: BP and Heart Rate in Children with ADHD

Meagan D. St. Amour, BSc [1,2] Deborah D. O'Leary, PhD [1] John Cairney, PhD [3,4] Terrance J. Wade, PhD [1]

1 Department of Health Sciences, Brock University
2 Faculty of Medicine, University of Toronto
3 Faculty of Kinesiology and Physical Education, University of Toronto
4 Department of Family Medicine, McMaster University

Corresponding Author:
Terrance J. Wade
Department of Health Sciences
Brock University
1812 Sir Isaac Brock Way,
St. Catharines, Ontario, L2S 3A1
Email: twade@brocku.ca

Acknowledgements:
This study was funded by the Heart and Stroke Foundation of Ontario (SDA2367).

Declaration:
All authors declare no conflicts of interest in this research.

Abstract

OBJECTIVE: This study examines the effect of ADHD diagnosis and stimulant medication for ADHD treatment on child heart rate (HR) and blood pressure (BP) in a community sample compared to children without ADHD.

METHODS: Data came from the HBEAT Study. 2,013 participants from 49 schools from southern Ontario in grades 5-8 were included. Linear regression analyses examined the effects of ADHD medications on systolic blood pressure, diastolic blood pressure, and heart rate adjusting for age, sex, and body mass index (BMI).

RESULTS: Compared to non-ADHD children and adjusting for age, sex and BMI, children with ADHD on stimulant medication had a 12.3 bpm higher HR, and 3.0 mmHg higher SBP and DBP (all statistically significant). Children with ADHD on no stimulant medication had no differences in HR and BP compared to those children without a diagnosis of ADHD.

CONCLUSION: Stimulant medications used to treat ADHD are associated with elevated HR and higher BP. While it is unknown if children on ADHD medications may be at risk for longer term cardiovascular issues, this study supports the need to examine the long-term consequences of ADHD medication.

MESH: ADD/ADHD, cardiovascular, children, medication, stimulants, blood pressure

Cardiovascular development begins with behaviours and experiences in childhood and adolescence including the lack of physical activity, improper nutrition, and obesity.[1,2] For example, the Young Finns Study found that LDL-C levels and SBP in childhood were associated with increased coronary artery calcium in adulthood, which is linked to coronary heart disease (CHD).[3] Additionally, the Bogalusa study found that as the number of cardiovascular risk factors increased throughout childhood, so too does the pathological evidence for later atherosclerosis in the aorta and coronary arteries.[4] Finally, the American Heart Association has shown that coronary artery calcium was present in adolescents and young adults in pathological autopsy studies.[4]

Recently, there is evidence to show that medications prescribed to children may have direct or indirect effects on their developing cardiovascular system.[5] Specifically, there has been some concern with respect to the effect of ADHD medication on children's cardiovascular health. With estimates of children with ADHD ranging from 3% to 11% in Canada[6] and the United States[7] this poses a serious concern. The most commonly prescribed medication for ADHD are central nervous (CNS) stimulants.[8] Stimulant prescription drugs include Adderall (dextroamphetamine), Ritalin (methyphenidate) and Concerta (methyphenidate). The National Institute of Mental Health reported that the overall prevalence of stimulant use among youth went from 0.6% in 1987 to 2.9% in 2002. However, the highest prevalence was among children 6-12 years old increasing from 4.2% in 1996 to 5.1% in 2008, and from 2.3% in 1996 to 4.9% in 2008 among 13-18 year olds.[9]

Studies that examine the effects of stimulant use on cardiovascular health primarily focus on adults taking ADHD medication, on those taking medication who already have an existing cardiovascular disease or condition, or, if they did examine children, on neurobehavioral effects rather than cardiovascular effects. We can find only three studies that examined the effects of stimulant use on cardiovascular indices in children.[10-12] The first study investigated ambulatory BP in children currently using stimulant medication for the treatment of ADHD and found heart rate to be 6 beats/minute and DBP to be 4 mmHg higher compared to those on placebo but the sample was only 11 children.[10] The second study did not examine BP and HR but used administrative records finding a 20% increase in risk for emergency department visits among children on stimulant medications compared to children not taking stimulants.[11] The final study compared children diagnosed with ADHD on stimulant medication versus nonstimulant ADHD medication and found a 3 mmHg increase in both SBP and DBP, and a 6 beats/minute increase in HR for both groups.[12] However, this study did not have a control group of children.

These studies suggest that there is some cardiovascular risk for children taking stimulant medication for ADHD but existing limitations prohibit a detailed examination as to whether it is the ADHD diagnosis, the medication, or both. The current study builds on previous clinical studies by using a community-level population to examine BP and HR among children with ADHD taking stimulant medication. Specifically, the research question assesses whether those children diagnosed with ADHD who are currently on stimulant medication have elevated levels of BP and HR compared both to children diagnosed with ADHD but not currently on any ADHD medications and to children without an ADHD diagnosis and not taking ADHD medication.

Methodology:

The data come from the Heart Behavioural and Environmental Assessment Team (HBEAT) study. The population consisted of children in grades 5-8 (10-14 years old) from 49 schools from a regional school board in Southern Ontario. The study was approved by both the university and the school district research ethics board. Informed written consent was obtained from the parents and verbal assent was obtained from the children to participate in the study. There were no exclusion criteria except for refusal to participate by the parent or child. The sampling strategy for the study was done in two phases. The first phase was done in the 2007/08 school year and included grades 6 to 8 students in all 49 schools. Of the estimated 5,484 children, 1,913 (35%) had positive parental consents and child assent and subsequently measured their BP, height, body mass, and hip and waist circumference. Of these, 69% (1,319) of parents returned completed questionnaires. The second phase occurred in 2011 and included 10 of the original 49 schools recruited for an intervention study. The estimated population size of grade 5 through 7 students was 1,044 of which 804 (77%) completed the consent and assent, BP, anthropomorphic measurements and questionnaires. The combined overall response rate of completed parent surveys and anthropometric measures across both phases was 32.6% (2,123). Any participant with one or more missing key study variables were removed from the study, reducing the combined sample size from 2,123 to 2,024. One participant who was diagnosed with developmental coordination disorder and was being treated with stimulant medication was removed from the analysis. Due to the small numbers, six children whose parents reported them taking non-stimulant ADHD medication and 4 participants whose parent reported them to be taking both stimulant and non-stimulant medication were removed. This reduced the total sample size to 2,013 subjects, 30.8% of the total student population and 94.8% of those who completed the cardiovascular assessment and parent questionnaire.

Information regarding children's diagnoses and current medication use was reported by the parent. Parents were asked whether their child has ever been diagnosed by a medical professional as having any of 25 possible diagnoses listed alphabetically including ADD/ADHD as well as a secondary question asking whether there was a diagnosis for any condition not listed above. Next, the parent was asked whether the child had taken any of 27 medications listed alphabetically in the previous month with a secondary question to collect information on medications not listed. After deleting those children whose parents reported non-stimulant medication use or both stimulant and non-stimulant medication use (see above), 99 were included in the analysis as being diagnosed with ADHD. Of those, 49 were prescribed stimulant medications to treat it including 11 on Adderall, 1 on generic dextroamphetamine, 28 on Concerta (methyphenidate), 7 on Ritalin (methyphenidate), and 2 on generic methyphenidate). The children were categorized into three groups based on their diagnosis and medication status including those with ADHD on stimulant medication (N=49), those with ADHD on no medication (N=50), and those with no diagnosis of ADHD and no stimulant or non-stimulant ADHD medication (N=1,914).

Measurements:

BP and HR were measured at the schools using the BPM-300, a one-step automatic oscillometric BP unit (BPM-300, VSM MedTech Devices Inc., Coquitlam, British Columbia, Canada) shown to be valid for use among children.[13] Participants were led in small groups to a quiet area where they sat quietly with feet flat on the floor for 15 minutes while answering two physical activity questionnaires. After the 15 minutes of rest, the children remained seated with their right arm positioned on an arm rest that was adjusted so that it was positioned at the midpoint of the sternum. The BP monitor took 6 independent sequential BP measurements at 1-minute intervals. The first 3 measurements were done to familiarize the participant with the process and sensation of cuff pressurization and were discarded. The last 3 measurements were averaged to provide SBP, DBP and HR. Height was measured without footwear and heels together using a portable stadiometer. Body mass was measured without footwear using a calibrated electronic medical scale. All anthropometric measures were taken three times and averaged.

Statistical Analysis:

Statistical analyses proceeded in two steps. First, the basic characteristics across the three groups of children are presented. Second, a set of regression analyses were conducted to examine SBP, DBP and HR comparing children with ADHD on stimulant medication and no medication to other children in the sample without ADHD. All regression analyses were adjusted for age, sex, and body mass index (BMI=kg/m^2).

Results

Of the 2,013 participants, the mean age was 11.8 years with slightly more females than males in the sample (Table 1). Those with ADHD were significantly more likely to be older and male, with no difference in average body mass index. Comparing those with ADHD across medication use (Table 2), there were no significant differences for age or BMI. More males than females were treated with ADHD medication.

Table 3 presents the regression analyses examining the differences in mean HR, SBP, and DBP comparing children with ADHD on stimulant medications and ADHD diagnosed children on no medication to all other children without ADHD and no ADHD medication. In the unadjusted regression analysis, those with ADHD on stimulant medication had significantly higher HR (11.9 beats/minute), SBP (3.0 mmHg), and DBP (2.8 mmHg) compared to those without ADHD. These differences remained significant after controlling for age, sex, and BMI. Those with ADHD on no medication did not differ significantly from the non-ADHD comparison group for HR or BP. Finally, among the covariates, higher age was significantly associated with lower HR but higher SBP while higher BMI was significantly associated with both higher SBP and DBP.

Discussion:

Children with ADHD in this community sample and currently taking stimulant medication had clinically and statistically significant elevated mean HR and both SBP and DBP compared to children without ADHD and not taking any stimulant medications. Moreover, those children diagnosed with ADHD but not currently taking stimulant medications had BP and HR roughly equivalent to children without ADHD. To our knowledge, this is the first study to use both a community-level sample to examine differences in BP and HR and also include a group of children with ADHD but not on stimulant medication compared to a non-ADHD, non-stimulant medication reference group. The results of this study both corroborate and contradict findings in previous clinical studies. Among children with ADHD in this sample taking stimulant medication, we found similarly elevated SBP and DBP.[10,12] However, we found elevated HR in children on stimulants to be about 12 to 13 beats/minute higher than both children with ADHD on no medication and non-ADHD children even after adjusting for sex, age, and BMI which were about twice as high as previous findings.[10,12] For example, Samuels et al. (2006), in a randomized, placebo-controlled, double-blind study of 11 subjects found statistically significantly higher heart rate (6 beats/minute) and DBP (3.9 mmHg) compared to the placebo treatment but a nonsignificant difference in SPB (2.8 mmHg).[10] While this sample size was small with only 11 participants likely influencing its statistical power, its findings suggest an association between ADHD medication and cardiovascular regulation. Just as importantly, the equivalent BP and HR between children with ADHD not currently on medication compared to the those without ADHD indicates that differences in these cardiovascular measures are due not a diagnosis of ADHD *per se* but to the use of stimulant medications. This population-level, community study extends the external validity of the previous clinical studies that have focused entirely on clinical populations of those with diagnosed ADHD as roughly 10% of children are diagnosed with ADHD and about 50% of these children (5% of all children) are taking prescribed stimulant medication for treatment.[6,7,9]

While it is still unknown as to whether the observed elevation in HR, SBP and DBP resulting from stimulant medication has adverse long term effects on the developing cardiovascular system of children, other long term cardiovascular studies have found a link between elevated BP in childhood and elevated BP in adulthood.[2,4] Based on these studies identifying a continuity for cardiovascular health from childhood and adulthood, our research, combined with previous clinical work, suggests a reason for concern. At this point, it is unclear as to whether this medication-induced, elevated HR and BP may put children at greater risk for longer-term hypertension in adulthood and at risk for developing tachycardiac arrhythmia's, coronary artery disease, and stroke compared to children not on any ADHD medication.[1] Additionally, as ADHD medications are usually administered chronically throughout childhood and, more recently, into adulthood with the increasing prevalence and treatment of adult-diagnosed ADHD,[10] the long-term effects of chronic stimulant ADHD medication use needs to be examined and compared in relation to potential cardiovascular changes. Based on the differences we observed in both BP and HR across groups, comparison of the long-term consequences appears to be justified.

Limitations of this study included the parental report of both ADHD diagnosis and medication use as well as the cross-sectional nature of the data. Specifically, diagnosis of ADHD and reported medication use was based on parent affirmation of listed inventories of possible medical diagnoses identified by a medical professional and prescribed drugs taken over the past month. We implicitly assume that the parent-reporting for both is accurate but we have no external means to confirm this unlike previous clinical studies. In addition, we were unable to assess the effect of differences in medication dosage which may influence elevations in both BP and HR. Also, as the study provides only a cross-sectional snapshot in time, we are unable to examine changes in these cardiovascular indicators over time both as medication regimens change and as children age. However, the strength of this study is the ability to move past existing clinical studies to examine HR and BP in a community sample of children diagnosed with ADHD on medication and on no medication and to compare these groups to children with no ADHD diagnosis. While it is unknown if children on stimulant medications may be at risk for longer term cardiovascular issues, this study indicates the need for longitudinal research to examine the potential longer-term consequences of stimulant use among children. Further work should confirm whether non-stimulant medication prescribed for ADHD also influences cardiovascular health as our sample of these children was too small to properly examine. Finally, future studies examining both children and adults could examine other, more sensitive and peripheral measures of arterial function and structure such as intima-media thickness, pulse wave velocity, baroreflex, and arterial stiffness as surrogate markers of cardiovascular health as these markers have been demonstrated to show changes more quickly in childhood to factors that affect cardiovascular development compared to ambulatory BP.[14-16] And these additional measures have also been shown to be independently and strongly linked to cardiovascular disease among adults.[17] This work would provide a more thorough assessment of the developmental processes that could establish any potential linkages to stimulant medication use during childhood that may have implications for longer-term risk of cardiovascular disease.[1]

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Table 1: Study Participant Characteristics

	Total Participants Without ADHD (N=1913)	Total Participants with ADHD (N=99)
Age (years)	11.8**	12.0**
Sex (% Male)	45.5***	67.6***
BMI (Kg/m^2)	20.4	20.9
On Stimulant Medication (%)	2.6***	49.5***

BMI=body mass index. ADHD=attention deficit hyperactive disorder. **$p<0.01$, ***$p<0.001$ (two-tailed)

Table 2: Comparing those children with ADHD diagnosis across medication use.

	On Stimulant Medication (N=49)	On No ADHD Medication (N=50)
Age (years)	11.9	12.1
Sex (% Male)	71.4*	64.0*
Mean BMI (kg/m^2)	20.1	21.8

BMI=body mass index. ADHD=attention deficit hyperactive disorder. * $p<0.05$ (two-tailed)

Table 3: Unadjusted and Adjusted Regression Analysis of Heart Rate (HR), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) on Children with ADHD on Stimulant Medication and on No Medication Compared to Children Without ADHD (N=2,013).

	HR (beats/minute)		SBP (mmHg)		DBP (mmHg)	
	Unadjusted b (se)	Adjusted b (se)	Unadjusted b (se)	Adjusted b (se)	Unadjusted b (se)	Adjusted b (se)
Children with ADHD on Stimulant Medication	11.9*** (1.6)	12.3*** (1.6)	3.0* (1.4)	3.0* (1.3)	2.8* (1.2)	3.0** (1.2)
Children with ADHD on no ADHD Medication	-1.0 (1.6)	-0.4 (1.6)	1.0 (1.4)	-0.5 (1.3)	0.3 (1.1)	0.01 (0.2)
Age		-1.4*** (0.3)		0.8*** (0.2)		0.2 (0.2)
Sex		-0.5 (0.5)		0.5 (0.4)		-0.5 (0.4)

BMI		0.1 (0.1)		0.7*** (0.1)		0.3*** (0.04)

b=unstandardized regression coefficient, se=standard error, ADHD=attention deficit hyperactive disorder, HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ (two-tailed).