UNDERSTANDING EFFECTS OF EXERCISE AND DIET TO IMPROVE MENTAL AND PHYSICAL HEALTH IN CHILDREN WITH BEHAVIORAL HEALTH DISORDERS

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Abstract

Approximately 13%–20% of children living in the United States experience a diagnosable behavioral health disorder (BHD) in a given year. Children with BHDs have elevated risk of poor mental and physical health outcomes. It is established that diet quality and physical activity (PA) levels are predictors of both chronic disease risk and behavioral health. Unfortunately, children with BHDs experience increased risk of poor diet and low PA relative to typically developing peers.

Given the high prevalence of BHDs and associated health disparities, this dissertation aims to help address major gaps in existing research. Chapter one investigates the effects on behavior of an RCT using cybecycling at a therapeutic school serving children with BHDs. We used mixed-effects logistic regression to assess relationships between intervention exposures and behavioral outcomes. We found that students successfully engaged in and had significantly lower risk of poor behavioral outcomes during the intervention, particularly on days they participated in aerobic exercise.

Chapter two examines exercise dose and changes in behavior, to better inform exercise prescription and interventions for children with a variety of BHDs. We used mixed-effects linear regression to examine dose-response relationships between aerobic exercise duration and intensity, and minutes of disciplinary time out of class and self-regulation scores. We found duration had an inverse, linear relationship with negative outcomes, and effects were amplified among children with an Attention Deficit-Hyperactivity Disorder (ADHD) diagnosis.
Chapter three considers roles played by ADHD diagnosis, stimulant use, and health behaviors in predicting children’s BMI change. We applied linear regression to longitudinal data from a nationally-representative cohort of children to assess associations between duration of stimulant use, ADHD diagnosis, and BMI change, and logistic regression to assess odds of poor diet and PA patterns between groups. We found stimulant use predicted greater BMI change in pre-/early adolescence, and children with ADHD were at elevated risk of poor dietary patterns regardless of medication status. Diet and PA did not mediate relationships between stimulant use and BMI change.

Each chapter provides important evidence to address chronic disease and behavioral health risks among children with BHDs in order to reduce existing health disparities.
# Table of Contents

Abstract ii

List of Figures v

List of Tables vi

Acknowledgements vii

Chapter 1 Cybercycling Effects on Classroom Behavior in Children with Behavioral Health Disorders: an RCT 1

Chapter 2 Dose-Response Effects of Exercise on Behavioral Health in Children and Adolescents 24

Chapter 3 ADHD Medication, Dietary Patterns, Physical Activity, and BMI in Children: A Longitudinal Analysis of the ECLS-K Study 47
List of Figures

Figure 1.1. Overview of Manville Moves cybercycling physical education curriculum. 6

Figure 1.2. Enrollment, randomization, and attrition flow diagram (CONSORT). 11

Figure 1.3. Percentage of participants exceeding CATRS-10 screening thresholds as a function of study condition. 13

Figure 2.1. Effect modification of the relationship between exercise duration and disciplinary time out of class (TOC) by ADHD status. 39

Figure 2.2. Effect modification of the relationship between exercise duration and self-regulation score (Conners Abbreviated Teacher Rating Scale-10 Item) by ADHD status. 39

Figure 3.1. Conceptual model of relationships between ADHD, medication, health behaviors, and BMI change in children. 52
List of Tables

Table 1.1. Baseline participant characteristics. 12

Table 1.2. Overall intervention and cybercycling PE effects on behavioral health outcomes compared with control condition. 15

Table 2.1. Description of baseline participant characteristics. 34

Table 2.2. Regression modeling results for continuous exercise exposures and measures for behavioral outcomes. 36

Table 3.1. Characteristics of the study population. 58

Table 3.2. Linear regression modeling results for BMI and BMI z-score outcomes. 61

Table 3.2. Logistic regression results for dietary patterns and physical activity outcomes in 5th grade. 62
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Finally, I would like to dedicate this dissertation to two people. First, to the memory of my friend, Kimberly Whitmore, who initially engaged me in this field of research and remains one of the kindest and most hopeful people I have ever known. Secondly, it is dedicated to my friend and former athlete, Patrick Cogan, who has not let a diagnosis of Friedreich’s Ataxia stop him from amazing feats of athletics and friendship, and who provided me with daily inspiration as I undertook my doctoral studies and completed this dissertation.
Chapter 1:

Cybercycling effects on classroom behavior in children with behavioral health disorders: an RCT

April Bowling, James Slavet, Daniel P. Miller, Sebastien Haneuse, William Beardslee, Kirsten Davison
Abstract

**Background and Objectives:** Exercise is linked with improved cognition and behavior in children in clinical and experimental settings. This translational study examined if an aerobic cybercycling intervention integrated into physical education (PE) resulted in improvements in behavioral self-regulation and classroom functioning among children with mental health disabilities attending a therapeutic day school.

**Methods:** Using a 14-week crossover design, students (N=103) were randomly assigned by classroom (k=14) to receive the 7-week aerobic cybercycling PE curriculum during fall 2014 or spring 2015. During the intervention, children used the bikes 2 times per week during 30-40 minute PE classes. During the control period children participated in standard non-aerobic PE. Mixed effects logistic regression was used to assess relationships between intervention exposures and clinical thresholds of behavioral outcomes, accounting for both individual and classroom random effects.

**Results:** Children experienced 32-51% lower odds of poor self-regulation and learning-inhibiting disciplinary time out of class when participating in the intervention; this result is both clinically and statistically significant. Effects were appreciably more pronounced on days that they participated in the aerobic exercise, but carryover effects were also observed.

**Conclusions:** Aerobic cybercycling PE shows promise for improving self-regulation and classroom functioning among children with complex behavioral health disorders. This school-based exercise intervention may significantly improve child behavioral health without increasing parental burden or health care costs, or disrupting academic schedules.
Introduction

The Centers for Disease Control and Prevention reports 13%–20% of children living in the US experience behavioral health disorders (BHD) in a given year; such disorders are among the most costly conditions to treat in children.\textsuperscript{1} Those experiencing BHD have other chronic health conditions (e.g., asthma, diabetes) more often than children without BHD.\textsuperscript{1,2}

Meanwhile, there is growing evidence that children with BHD are less likely to engage in aerobic exercise/physical activity than their typically developing peers.\textsuperscript{3,4} This can occur for many reasons including exclusion from sports due to behavioral problems, comorbid sensory issues, delayed motor skills, and anxiety.\textsuperscript{4,5} Low engagement in aerobic activity is linked with lower fitness, which may then further discourage exercise participation.\textsuperscript{3}

Low engagement in exercise is particularly troubling given these children’s increased risk for chronic diseases and evidence that exercise may have cognitive, behavioral and emotional benefits. Relatively short bouts have been shown to improve impulsivity and mood state among typically developing children and those with single BHD such as attention deficit hyperactivity disorder (ADHD), autism (ASD), or depression.\textsuperscript{6–8} Intensity has also been linked to cognitive effects in children; one study found that vigorous intensity exercise resulted in better executive function outcomes than moderate/light intensity exercise.\textsuperscript{9}

These findings emphasize the importance of finding aerobic exercise modalities that overcome the engagement challenges facing this population. However, this research has not been translated into special education settings, or extended to examine effects in children with heterogeneous BHD. Thus, in this study we examine if a cybercycling PE intervention, which
successfully engages children with BHD in aerobic exercise,\textsuperscript{11} is linked to improvements in behavioral self-regulation and classroom functioning relative to standard non-aerobic PE.

**Methods**

**Setting and Participants**

The study was conducted at a therapeutic day school affiliated with Harvard Medical School. The school enrolls about 110 children each year in kindergarten through 10\textsuperscript{th} grade year with diagnosed BHD, many of whom have learning disabilities, but does not serve children with intellectual disabilities.

Students are predominantly male and have multiple diagnoses; in an average school year, about 40\% of enrolled students are diagnosed with ASD, 60\% with ADHD, 40\% with an anxiety disorder, and 30\% with a mood disorder. There are 14 classrooms, each with a head teacher, an assistant teacher, and a classroom counselor. Students are engaged with a variety of in-school service providers including psychologists, occupational therapists, and speech pathologists.

**Intervention Design**

A 14-week crossover design was utilized. Children were randomly assigned by classroom to receive the 7-week intervention during fall or spring, with a 10-week washout period between treatment arms. A simple random number generator was used to assign 7 classes to the fall treatment; the remainder served as the fall control group and received treatment in the spring. Detailed information on the intervention and its development is published elsewhere.\textsuperscript{10}

The intervention, known as *Manville Moves*, featured a progressive and aerobically challenging PE curriculum using virtual-reality exergaming stationary bicycles (cybercycles).
The curriculum overview is contained in Figure 1.1. Existing PE efforts at the school were not successful at engaging the majority of children in extended bouts of aerobic exercise. Therefore, the exercise modality was selected to optimally engage children with complex BHD who, again, often face exercise engagement challenges such as sensory processing disorders, low fitness levels, socialization challenges, and motor delays; the curriculum was designed to gradually accustom participants to riding for extended durations and higher intensities.

During the intervention, children used the bikes 2 times per week during 30-40 minute PE classes, starting at 10 minutes riding duration and building to over 20 minutes over the 7 week period. During the control period, children continued to participate in standard PE programming (2 times/week x 30-40 mins). Standard PE is focused on games to build socialization and team skills as well as motor skill acquisition through activities such as basketball shooting; thus there are only short bouts of aerobic exercise and many students struggle to remain engaged even with extensive staff attention.

The study protocol was reviewed/approved by the Harvard T.H. Chan School of Public Health Institutional Review Board. The intervention was co-designed by school personnel and the research team and implemented during the 2014-2015 academic year. The school elected to integrate the intervention into school programming; thus an opt-out consent process was utilized. Demographic/baseline data were obtained using an online caregiver survey after an active consent process.
### CURRICULUM WEEK #1

<table>
<thead>
<tr>
<th>PE Class #1</th>
<th>PE Class #2</th>
</tr>
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<tbody>
<tr>
<td>Minimum Duration</td>
<td>Target Intensity</td>
</tr>
<tr>
<td>10 Minutes</td>
<td>Light to Moderate</td>
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### CURRICULUM WEEK #2

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<td>Minimum Duration</td>
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<td>12 Minutes</td>
<td>Light to Moderate</td>
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### CURRICULUM WEEK #3

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<td>Minimum Duration</td>
<td>Target Intensity</td>
</tr>
<tr>
<td>15 Minutes</td>
<td>Moderate</td>
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</table>

### CURRICULUM WEEK #4

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</tr>
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<td>18 Minutes</td>
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### CURRICULUM WEEK #5

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<td>Target Intensity</td>
</tr>
<tr>
<td>15 Minutes</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

### CURRICULUM WEEK #6

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<tbody>
<tr>
<td>Minimum Duration</td>
<td>Target Intensity</td>
</tr>
<tr>
<td>20 Minutes</td>
<td>Moderate to Vigorous</td>
</tr>
</tbody>
</table>

### CURRICULUM WEEK #7

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<th>PE Class #2</th>
</tr>
</thead>
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<tr>
<td>Minimum Duration</td>
<td>Target Intensity</td>
</tr>
<tr>
<td>15 Minutes</td>
<td>Vigorous</td>
</tr>
</tbody>
</table>

**Figure 1.1.** Overview of *Manville Moves* cybertesting physical education curriculum.
Objectives

The study’s first research aim was to determine if students had improved classroom functioning demonstrated through reduced disciplinary time out of class, as well as improved self-regulation scores when participating in the intervention PE curriculum compared with standard non-aerobic PE. Thus, the first aim was to assess the combined acute and chronic effects of exercise, along with programmatic effects of the intervention, over the duration of 7-week intervention compared with the 7-week control condition.

The second research aim was to specifically assess the acute effects of exercise by examining behavioral changes only on days that children participated in the aerobic cybercycling PE intervention compared with the control condition.

Exposure and Outcomes

*Exercise exposure* was measured using the data captured by the bicycles via student-specific login codes. Data compiled for each riding bout included timestamp, average heart rate, and minutes of riding. Student refusals to ride, as well as any occurrences of mechanical or electrical failure, were documented on paper. It was not feasible to collect objective exercise data for the control condition, since children would not tolerate wearing heart rate monitors or accelerometers. However, the standard PE curriculum did not include programming targeting aerobic exercise while children were in the control condition. Additional information on fidelity of implementation and student engagement is described elsewhere.\textsuperscript{11}

*Behavioral self-regulation* was operationalized using the Conners Abbreviated Teacher Rating Scale (CATRS-10), a validated screening instrument for behavioral problems related to inattention, impulsivity/hyperactivity, and emotional lability.\textsuperscript{12,13} Classroom counselors
completed the CATRS-10 at the end of each school day for each student. The instrument consists of 10 statements regarding the child’s behavior rated on a 4-point Likert scale, with a total score ranging from 0 to 30. A score of 15 or higher has been the standard for screening children with symptomatology at a level of clinical concern. Equivalent screening thresholds were used for the emotional lability subscale (4 questions, ≥6 out of possible 12) and impulsivity subscale (6 questions, ≥9 out of possible 18).

Because the classroom counselors accompanied students to PE, it was not possible to blind them to participants’ treatment group assignment. However, the counselors were not explicitly informed of the study objectives and received no incentives dependent on the participants’ treatment group assignment. They were also prevented from viewing previous recordings of CATRS-10 in order to help prevent manipulations of variability based on prior measurements. The study coordinator for the school reviewed counselor reporting records on a weekly basis to ensure compliance. A research assistant was also assigned to check CATRS-10 scores for variability on a bi-weekly basis; no statistically significantly decrease in reporting variability was observed during the course of the study. In addition, no differences in reporting patterns were observed on days when floating counselors filled in for classroom counselors who were absent. Of note, the floating counselors did not attend PE sessions with the class and therefore were not aware of their treatment status.

Classroom functioning was operationalized based on disciplinary time out of class (TOC). When teachers determined a child must leave class due to unacceptable behavior, counselors recorded the event using the mobile survey platform to enter the student identification code and number of minutes for each TOC event as it occurred. This measure yields minutes of TOC per day and number of TOC events per day for each student. Teachers follow a school-
wide policy when determining whether a child receives TOC and unlike counselors, were blinded to treatment status. Because recording TOC has been a longstanding procedure, and any TOC must be reported to parents, we feel that this measure is less vulnerable to subjective interpretation or bias if treatment status was learned by teachers.

School clinicians established a priori thresholds for clinically relevant TOC per day that constituted either a disruption to a student’s ability to learn classroom material (defined as 1 or more events per day regardless of cumulative time or 10 or more minutes per day regardless of total number of events), or prevented meaningful learning for that day (defined as 5 or more events per day or 90 or more minutes per day).

Sample Size and Analytical Plan

Because exposures and outcomes were measured each day, the relevant unit of analysis for the study is a child-day. A logistic-normal mixed effects regression model\textsuperscript{17} was used to assess relationships between intervention exposures and clinical thresholds of behavioral outcomes accounting for both individual and classroom random effects. Outcome variables were dichotomous indicators of whether or not a child exceeded clinical or screening thresholds for either classroom functioning, measured by TOC, or self-regulation using the CATRS-10.

The maximum possible sample size was 109 based on school enrollment, and a priori power calculations indicated that a sample of at least 75 students would provide power > 90% to detect the small to moderate effect size (d=.3 to d=.5) in executive functioning evident in literature.\textsuperscript{6,18,19} Given nearly universal participation, daily outcome measurements, cross-over design, and minimal attrition, the sample size was more than adequate. The number of child-days varied by outcome and are described in the results section.
The primary models tested aim 1 (i.e., the overall treatment effect of the intervention) for each outcome measure. Treatment status and treatment order were included in each model as independent variables to evaluate overall treatment effects while accounting for potential seasonality/contamination effects. The secondary models assessing aim 2 (i.e., the acute exercise effects of the intervention) additionally included terms indicating whether a child participated in the cybercycling PE class intervention on that day. Finally, the models were also run introducing a dichotomous variable representing whether the students used the bikes in the virtual course mode or the video gaming mode to test for potential exergaming effects. All statistical analyses were conducted in STATA 13.1, using a two-tailed significance level of \( P = 0.05 \).

Results

Demographic characteristics

Figure 1.2 shows the CONSORT enrollment, randomization and attrition flow diagram. The final enrollment was \( N=103 \) students; the fall intervention arm included \( n=51 \) students in 7 randomly assigned classrooms, and the spring intervention arm included \( n=52 \) students in the remaining 7 classrooms. Baseline demographic data is contained in Table 1.1. Participants were 83.5% males, and ages ranged from 7 to 16 years of age with a mean of 11.8 years of age. No adverse events occurred during the intervention.
Figure 1.2. Enrollment, randomization, and attrition flow diagram (CONSORT).
Table 1.1: Baseline participant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N, %)</td>
<td>86 (83.5)</td>
</tr>
<tr>
<td>Age (mean, range)</td>
<td>11.8 (7-16)</td>
</tr>
<tr>
<td>Multiple Diagnoses (N, %)</td>
<td>46 (57.5)</td>
</tr>
<tr>
<td>Taking Medication (N, %)</td>
<td>39 (50.7)</td>
</tr>
<tr>
<td>Race/Ethnicity (N, %)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>White</td>
<td>68 (85.0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Eligibility Free/Reduced Cost Lunch (N, %)</td>
<td>23 (29.9)</td>
</tr>
<tr>
<td>Met Fitness Standards at Baseline (N, %)</td>
<td>11 (17.8)</td>
</tr>
</tbody>
</table>

1 Subset of students for whom a guardian returned a baseline survey (n=80).
2 One family declined to answer so categories do not add to 100%.
3 Subset of students who participated in baseline fitness testing (n=62).

Documentation of the exposure and outcome variables

There were 913 cybercycling PE days; average cycling duration in class was 16.1 (±5.3) minutes, while average heart rate was 146.6 (±25.3) beats per minute. This indicates that students achieved sustained aerobic exercise during cybercycling PE classes on average.

For the classroom functioning outcome of TOC there were 6,419 observations recorded over both intervention periods (fall n= 3318, $\bar{x}$=17.44±50.11; spring n= 3101, $\bar{x}$=17.48±54.18), of which there were 2,122 instances of students having one or more removals from class in a day (fall n=1205, spring n= 917). There were 5,252 observations of CATRS-10 scores recorded (fall n= 2378, $\bar{x}$=9.03±7.02; spring n=2874, $\bar{x}$=8.50±6.52); of those, 955 exceeded the clinical screening threshold for disruptive behavior (fall n=475, spring n=480). Treatment order was not
found to be significant in any of the models. Individual and classroom random effects are controlled for in all analyses; children serve as their own controls and group level differences in outcome variables between fall and spring do not affect the validity of analyses. Compared to days in the control condition, percentages of children exceeding screening thresholds for overall CATRS-10 score and both impulsivity and emotional lability sub-scores declined on days in the intervention condition, and were lowest on days when the children participated in cybercycling PE class (Figure 1.3). Post-hoc tests found no evidence of time of day effects for morning versus afternoon PE classes.

Figure 1.3. Percentage of participants exceeding CATRS-10 screening thresholds as a function of study condition.
Models testing overall intervention effect (aim 1)

Results (Table 1.2, column 1) show clinically significant intervention effects. While in the 7-week intervention, students experienced significantly reduced odds of exceeding screening thresholds for total CATRS-10 score (OR=0.68, 95% CI: 0.57, 0.81), emotional lability sub-score (OR=0.64, 95% CI: 0.52, 0.77), and impulsivity/hyperactivity sub-score (OR=0.49, 95% CI: 0.36, 0.67), relative to when they participated in standard non-aerobic PE (i.e., the control condition). Students also experienced significantly lower odds of having 5+ TOC events (OR=0.54, 95% CI: 0.32, 0.91). The overall treatment effect was not significant for learning disruptive TOC outcomes (1+ events, 10+ minutes) or preclusive to learning TOC minutes (90+ minutes).
Table 1.2: Overall intervention and cybercycling PE effects on behavioral outcomes compared with control condition.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall Intervention Effect(^a) (Adjusted OR, CI)</th>
<th>Intervention Effect on Cybercycling PE Days(^b) (Adjusted OR, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exceeds Total CATRS-10 Screening Threshold</td>
<td>0.68 (0.57, 0.81)</td>
<td>0.29 (0.14, 0.61)</td>
</tr>
<tr>
<td>Exceeds Impulsivity/Hyperactivity Threshold</td>
<td>0.49 (0.36, 0.67)</td>
<td>0.28 (0.13, 0.59)</td>
</tr>
<tr>
<td>Exceeds Emotional Lability Threshold</td>
<td>0.64 (0.52, 0.77)</td>
<td>0.24 (0.11, 0.53)</td>
</tr>
<tr>
<td>1+ TOC events/day</td>
<td>1.04 (0.92, 1.18)</td>
<td>0.43 (0.26, 0.72)</td>
</tr>
<tr>
<td>5+ TOC events/day</td>
<td>0.54 (0.32, 0.91)</td>
<td>0.10 (0.02, 0.61)</td>
</tr>
<tr>
<td>10+ TOC minutes/day</td>
<td>1.03 (0.89, 1.18)</td>
<td>0.50 (0.29, 0.89)</td>
</tr>
<tr>
<td>90+ TOC minutes/day</td>
<td>1.04 (0.84, 1.31)</td>
<td>0.34 (0.14, 0.84)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for treatment order and accounting for random effect of individual and random effect of classroom assignment. Odds relative to any day in the control condition.

\(^b\) Adjusted for treatment order, elective biking days, and non-adherent PE class days in the treatment condition. Odds relative to non-biking days in the control condition.

TOC=Disciplinary Time Out of Class
OR=Odds Ratio
CI=Confidence Interval

Models testing acute exercise effects (aim 2)

The effects of acute exercise were significantly more pronounced than the overall intervention effects (Table 1.2, column 2). On days that students participated in an intervention PE class, they experienced clinically and statistically significantly reduced odds of exceeding screening thresholds for total CATRS-10 score (OR=0.29, 95% CI: 0.14, 0.61), emotional
lability sub-score (OR=0.24, 95% CI: 0.11, 0.53), and impulsivity/hyperactivity sub-score (OR=0.28, 95% CI: 0.13, 0.59), relative to the control condition. Acute effects of cybercycling PE class also resulted in significantly reduced odds of both learning-disruptive and preclusive TOC events (OR=0.43, CI:0.26, 0.72; OR=0.10, CI: 0.02, 0.61) and minutes (OR=0.50, CI: 0.29, 0.89; OR=0.34, CI: 0.14, 0.84). Treatment order and video gaming mode were not significant in any of the models.

**Discussion**

This study provides compelling evidence that children and adolescents with multiple, heterogeneous BHD in a school setting can successfully engage in and experience behavioral benefits from an aerobic, cybercycling PE curriculum. Across the intervention period, odds that children would display clinically disruptive behaviors including impulsivity and emotional lability were 32% to 51% lower than during the control condition. These effects strengthened on days when children participated in an intervention cybercycling class; here odds of disruptive levels of behavioral dysregulation declined between 71% and 76% relative to the control condition. Acute exercise led to significant declines in odds of receiving learning disruptive and preclusive amounts of disciplinary TOC. These results build on previous research showing positive effects of aerobic exercise on mood and impulsivity in children, and translate those findings into a program implemented in a real world setting with children with multiple BHD.

The primary research aim was to determine whether intervention participation resulted in improved behavioral outcomes for students; this was the case, however, effects were more pronounced on days when the children participated in the structured, aerobic cybercycling PE classes. So while there seem to be chronic exercise and programmatic effects of this intervention
on behavioral self-regulation and classroom functioning even on days when children did not bike, acute exercise is the primary driver of the intervention effect. This finding is consistent with prior studies and proposed mechanisms by which neuroendocrine and reticular-activating systems affect mood and functioning in areas of the brain related to executive function and impulse control.21

Although it was impossible to blind counselors to the intervention condition, we feel risk of bias in recording student behaviors due to knowledge of treatment status was low. Neither teachers nor counselors were aware of the primary study hypotheses. Also, the outcome of disciplinary TOC is determined by classroom teachers who were not aware of treatment condition. Post-hoc tests for bias included comparison of CATRS-10 by blinded (floating) and non-blinded counselors, which indicated no reporting differences, and examination of scores on days students electively rode. If counselors were aware of the hypothesis/biased in reporting, scores should have been lower for children on those days as they were for cybercycling PE days since counselors accompany them to ride; in fact point estimates indicated worse scores than on non-riding days (not statistically significant).

In addition to aerobic exercise, the cybercycling PE classes may hold several other advantages over standard PE programming. They require fewer transitions, which are often challenging to children with BHD. Also, the cybercycling PE allowed students to avoid peer judgements of performance, since other students could not see their performance data unless they share it. It was also less noisy and chaotic than standard PE classes.11 However, it is important to note that standard PE class may confer its own benefits, including motor skill acquisition, team sports practice, and socialization. Cybercycles are also relatively expensive; since the key is
overcoming aerobic exercise engagement barriers, other modalities should be explored with similar populations.

Because the intervention was implemented as part of school programming, participation was nearly universal; therefore, selection biases that generally accompany active participant recruitment and consent protocols were avoided. The generalizability of the results is enhanced because participants had a wide variety of diagnoses, including complex comorbidities. Finally, this study demonstrates strong ecological validity because the intervention was conducted within existing school schedule and staffing. This improves potential for scale-up/dissemination in more diverse settings catering to children with BHD.

Despite these strengths, the generalizability of the results is limited by the setting and population targeted. Therapeutic day schools serve children who have been unsuccessful in public school special education environments. Thus, findings from this study are limited to students with substantial BHD. Future research could test the intervention in special education programs in public schools is needed to determine if a broader group of children may benefit from the program.

Despite overall cuts to PE class time allocation\textsuperscript{22}, efforts are taking place across the United States to allow movement in classrooms and facilitating improved learning and behavior.\textsuperscript{23} However, while children with BHD may most benefit from the effects of aerobic exercise, they are least likely to be easily engaged in such activities. This study shows that a cybercycling PE curriculum can successfully engage children with a variety of complex BHD in high-quality aerobic exercise, and as a result, they experience significant improvements in
important behavioral measures. Critically, such a curriculum can successfully affect student behavior within existing school programming with short durations and low frequency.

Acknowledgements

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Conflict of Interest

All authors have indicated they have no potential conflicts of interest to disclose.

Clinical Trials Registration

Clinical Trials Registry, United States National Institutes of Health. Clinical trials number NCT02766101. Web link:

https://clinicaltrials.gov/ct2/show/NCT02766101?term=NCT02766101&rank=1
References


Chapter 2:

Dose-Response Effects of Exercise on Behavioral Health in Children and Adolescents

April Bowling, James Slavet, Daniel P. Miller, Sebastien Haneuse,
William Beardslee, Kirsten Davison
Abstract

Purpose: Aerobic exercise appears to positively affect behavioral health in children. However, little research has been conducted on dose-response effects among those with behavioral health disorders (BHD). This study uses data collected from an RCT to test the effects of cybercycling on behavioral outcomes in children with BHD attending a therapeutic school. We examine dose-response relationships between duration and intensity of cybercycling and minutes of disciplinary time spent out of class and self-regulation scores; additionally we examine potential effect modification by Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosis.

Methods: A 14-week crossover design was used. Children (N=103, 83.5% male, age 11.8±2.3) were randomly assigned by classroom to receive the 7-week intervention during fall or spring, during which they used the bikes 2 times per week in physical education class. Real-time data on exercise duration was collected via the bicycles. The Conners Abbreviated Teacher Rating Scale for self-regulation and minutes of disciplinary time out of class (TOC) were recorded daily for each child. Ride duration and average heart rate were treated as continuous predictors of outcomes using mixed effects linear regression.

Results: For every 10 minutes of riding, children had an associated decline of 10.7 minutes of TOC (p<0.001) and 1.2 points improvement in self-regulation score (p<0.001). For each increase of 10 beats per minute average heart rate children had an associated decline of 1.3 minutes (p=0.05) and 0.21 points (p<0.05). The effect of duration on behavioral outcomes was significantly modified by ADHD diagnosis.
**Conclusion:** Both duration and intensity of aerobic exercise appeared to have significant, linear relationships with improved behavioral outcomes among children with a variety of BHD; children with ADHD may experience the greatest benefits of riding for longer durations.
**Introduction**

Childhood behavioral health disorders are common and increasing in prevalence in the United States and many other countries (15, 18). While the neurodevelopmental diagnosis Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common, behavioral health diagnoses in children also include autism spectrum disorders, depression, bipolar, and disruptive behavior disorders among many others (17). According to the Center for Disease Control’s most recent report on pediatric mental health surveillance, 13%–20% of children living in the United States experience a diagnosable behavioral health disorder in a given year, and lifetime rates of comorbid mental health diagnoses may exceed 40% (17).

There is a growing body of evidence that exercise exposures, particularly bouts of aerobic exercise, may positively affect behavior, mood and cognition in children both with and without behavioral health disorders (12). A recent systematic review of 8 randomized controlled trials found generally positive, if somewhat weak effects of exercise on psychosocial functioning in children (12). A meta-analysis of 19 studies investigating effects of physical activity on executive function in children, adolescents and adults found a significant moderate effect size for acute exercise exposures (23).

While a comprehensive review of pathways is beyond the scope of this article, research suggests that acute aerobic exercise affects neurotransmitter secretion and reuptake and is associated with changes in neural activation patterns, while chronic exercise appears to promote neurogenesis (14, 22). Although studies are sparse, there is also evidence that children with ADHD may selectively experience certain benefits to executive function and decreased impulsivity from exercise (19, 20). This would make sense, given that exercise affects the same
catecholamine pathways targeted by stimulant medication to produce attentional and behavioral improvements.

Unfortunately, there is also mounting evidence that like children with other types of disabilities, those with behavioral health disorders are less likely to engage in aerobic exercise and/or moderate to vigorous physical activity (MVPA; hereafter simply described as exercise) and thus are less likely to experience these potential benefits (13). A variety of barriers to exercise have been documented in these populations including exclusion from traditional sporting leagues due to behavioral problems, oppositional responses to attempts by parents to manage health behaviors, sensory disorders and anxiety that discourage exercise engagement, comorbid gross motor delays, and weight gain and perceived exertion changes associated with certain psychiatric medications (21).

Given these challenging barriers to exercise engagement, it is crucial to examine whether exposures of shorter duration and lower intensity improve behavioral health outcomes in order to improve both efficacy and feasibility of interventions and exercise prescriptions. While many studies have shown overall treatment effects on behavioral outcomes from specific exercise and physical activity interventions among children with behavioral health disorders, effects have varied significantly across different treatment modalities and intervention approaches (1, 3, 10).

For example, Davis et al. (7) and Hillman et al. (11) both used 20 minute bouts of MVPA and found significant effects on self-regulation among typically developing children. Among children with ADHD, Gawrilow et al. (9) found improvements to response inhibition after acute trampoline jumping bouts of only 5 minutes, Pontifex et al. (20) found improvements to a variety of neurocognitive and executive function measures after 20 minutes of MVPA on a treadmill,
and Chang et al. (4) found similar results after 30 minutes of running. In contrast, Oriel et al. (16) found that 15 minutes of running was not associated with improved classroom functioning in children with autism spectrum disorders. We are not aware of other studies of exercise and classroom behavioral outcomes that used exercise exposures of less than 45 minutes, a difficult amount to achieve given the barriers to exercise engagement in this population.

Also of importance, most current research has primarily focused on typically developing children or those with a single behavioral health diagnosis, and thus lacks generalizability to children with multiple behavioral health challenges. This also contributes to the existing inability to advise parents and clinicians whether shorter and less intense exercise exposures elicit significant behavioral improvements for diverse populations, despite a demand for such knowledge (26). This lack of understanding of real-world dose-response relationships constitutes a critical evidence gap that negatively affects the treatment of these disorders and inhibits the design of effective programming in therapeutic schools, special education classrooms and clinical settings.

This article reports an exploratory follow-up investigation of the dose-response relationship between acute exercise duration and intensity and behavioral outcomes post-exercise among children with heterogeneous behavioral health disorders who participated in the Manville School Cybercycling and Behavior Randomized Controlled Trial (Manville Moves). Manville Moves was designed to examine if an aerobic cybercycling PE intervention was linked to improvements in behavioral self-regulation and classroom functioning relative a control condition among 103 children with behavioral health disorders. The RCT found that participation in the intervention resulted in greatly reduced clinically disruptive behaviors and
learning disruptive disciplinary time out of class among children compared to the control condition (reference pending, under review at Pediatrics).

Building on these results, in the current study we examine relationships between behavioral outcomes and continuous measures of exercise duration and intensity. Based on previous research, we hypothesized that both increased exercise duration and intensity would have inverse relationships with negative behaviors. Also, while Manville Moves was not designed or powered to examine modification by individual child behavioral health characteristics, it provides an opportunity to conduct hypotheses-generating analyses into possible effect modification of exercise-behavior relationships by children’s ADHD diagnosis status, which as described previously, may plausibly alter neurological and endocrine responses to exercise.

Methods

Setting and Participants

The study design, fidelity of implementation, and treatment effects of the Manville Moves RCT has been described extensively in other publications (2, 8). A total of 103 children attending a therapeutic day school participated in the original study, from which this investigation draws its data. Participants ranged from 7 to 16 years of age, and all had at least one diagnosed behavioral health disorder, with the most prevalent diagnoses being ADHD, autism and anxiety. The study protocol was reviewed and approved by the Harvard T.H. Chan School of Public Health Institutional Review Board. The school integrated the PE curriculum into school programming; thus, the study used an opt-out consent process, and all children enrolled in the school participated in the study with the exception of one child who had a medical
exemption from PE class. Following an active consent process, caretakers of the participants filled out a survey, offered both online and via hard copy, which collected data on their child’s baseline physical activity levels, diagnoses, medication types, and family demographics. Surveys were returned for 80 (77.7%) participants.

**Design and Procedures**

The RCT utilized a crossover, group-randomized controlled design. Children were randomly assigned by classroom to receive the 7-week intervention during fall or spring, with a 10-week washout period between treatment arms. The intervention featured an aerobically challenging PE curriculum using virtual-reality exergaming stationary bicycles (cybercycles). During the intervention, children used the bikes 2 times per week during 30-40 minute PE classes. **Figure 1.1** (Chapter 1) contains an overview of the curriculum. Because of the inclusion of “choice days” in the curriculum, which had very short or no minimum riding duration or intensity targets, there was not a floor effect on riding exposures presented by the curriculum. This study utilizes the exercise exposure and behavioral outcome data measured on cybercycling PE days during the RCT. Thus, while the original study utilized cross-over control groups, as a dose-response investigation the current study only utilizes data from the intervention groups.

**Exercise Duration and Intensity**

Data on continuous measures of exercise duration (minutes of riding) and intensity (average HR) were collected via the cybercycles during PE class (Expresso HD Upright Bike™, Interactive Fitness, Santa Clara, CA) using unique login codes for each participant. Participants entered their codes prior to each ride under the direction of staff, and data were directly uploaded into the database. HR was measured continuously via handlebar sensors and recorded as an
average for each riding bout. While the preferred measurement approach would have been the use of chest-strap HR monitors, these were not tolerated by the study population, and thus the handlebar sensors were used instead.

Behavioral Outcomes

Behavioral self-regulation score (SRS): Classroom counselors completed the Conners Abbreviated Teacher Rating Scale – 10 Item at the end of each school day for each student. This instrument is a commonly used, well-validated measurement instrument for behavioral problems related to hyperactivity/impulsivity and emotional lability, and is utilized to screen for ADHD.(6, 24) Higher scores on the Conners scale indicate worse behavior problems. Over the 14-week study, 5,250 Conners ratings were recorded using a mobile survey platform.

Disciplinary Time Out of Class (TOC): Time spent out of class is negatively related to learning outcomes, and was considered an important indicator of overall classroom behavior and functioning.(8) Staff recorded all events where students were asked to leave the academic classroom by a teacher due to unacceptable behavior, including the number of minutes that the child was out of the classroom. Classroom counselors used a mobile survey platform to enter the student identification code and number of minutes for each disciplinary event as it occurred. Over the 14-week study, 6,489 observations of TOC were recorded, including one recording of zero minutes for each day that a student did not have time out of class.

Statistical Analyses

Analyses examined the effect of exercise duration and intensity on behavioral self-regulation and classroom functioning. As previously noted, exercise duration and intensity were modeled as continuous predictors of the outcomes. Multilevel mixed-effect linear regression
was conducted to assess relationships between behavioral outcomes and both duration of exercise and intensity of exercise while accounting for both random individual and classroom effects, since individuals consistently biked within their assigned class.

Separate models were constructed for each outcome and included both exposure types to control for covariation of duration and intensity. The primary models were unadjusted (model 1). Models were tested for non-linear effects, and secondary analyses were also conducted to test for effects of time and increased fitness over time on relationships between exercise exposure and behavior. This was accomplished by including an interaction term between time (week of study) and exercise exposure. Models were then adjusted for demographic and health characteristics of children including race, sex, age, ADHD diagnosis, and psychiatric medication use (model 2). Finally, models were examined for effect modification by ADHD (model 3). All statistical analyses were conducted in STATA 13.1, using a two-tailed significance level of $P = 0.05$.

Results

Participants’ engagement in aerobic exercise through cybercycling PE classes during the intervention is detailed extensively elsewhere (2). There were N=103 participants who took part in both the control and the intervention condition; demographic and health characteristics at baseline are shown in Table 2.1. Over 779 PE class riding bouts, the average cycling duration in class was 16.1 ($\pm$5.3) minutes, while average heart rate was 146.6 ($\pm$25.3) beats per minute (approximately 77% of theoretical maximum threshold based on studies in similar populations) (3). Modeling results showed no evidence of non-linearity, and there was no significant effect of fitness on behavioral outcomes for either exercise duration (SRS: $\beta=-0.03$, 95%CI: -0.16 – 0.10;
TOC: $\beta=-0.84, 95\%CI: -1.86 - 0.18$ or intensity (SRS: $\beta=0.07, 95\%CI: -0.05 - 0.18$; TOC: $\beta=-0.55, 95\% CI: -1.49 - 0.39$). Thus fitness effect (i.e., week of study) was omitted from the final models.

Table 2.1. Description of baseline participant characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N, %)</td>
<td>86 (83.5)</td>
</tr>
<tr>
<td>Age (mean, range)</td>
<td>11.8 (7-16)</td>
</tr>
<tr>
<td>Multiple Diagnoses (N, %)</td>
<td>46 (57.5)</td>
</tr>
<tr>
<td>ADHD Diagnoses (N, %)</td>
<td>46 (57.5)</td>
</tr>
<tr>
<td>Taking Medication</td>
<td></td>
</tr>
<tr>
<td>Not Medicated</td>
<td>22 (47.8)</td>
</tr>
<tr>
<td>Taking Medication (N, %)</td>
<td>39 (50.7)</td>
</tr>
<tr>
<td>Race/Ethnicity (N, %)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>White</td>
<td>68 (85.0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (5.0)</td>
</tr>
</tbody>
</table>

1Subset of students for whom a guardian returned a baseline survey (n=80)
2Either singular or comorbid diagnosis
3One family declined to answer so categories do not add to 100%
Dose-Response Relationship Modeling

Multilevel mixed-effects linear regression results are shown in Table 2.2. In both the crude (model 1) and adjusted models (model 2), minutes of riding had a significant, inverse linear relationship with both self-regulation score and disciplinary time out of class minutes. In the adjusted model, holding average HR constant, each additional 10 minutes of riding were associated with an 10.7 minute reduction in disciplinary time out of class (95%CI: -16.8, -5.2) and 1.2 (95%CI: -1.9, -0.5) point decrease in self-regulation score.

Intensity showed a similar, but weaker association with outcomes. In the adjusted model, each additional 10 bpm was associated with a 1.3 minute decline in disciplinary time out of class (95%CI: -2.7, 0.0) and a 0.2 (95%CI: -0.4, 0.0) point decrease in self-regulation score.
Table 2.2. Regression modeling results for continuous exercise exposures and measures of behavioral outcomes.

<table>
<thead>
<tr>
<th>Outcome: Self-regulation Score</th>
<th>Model 1 Unadjusted (N=103)</th>
<th>Model 2 Adjusted (N=80)</th>
<th>Model 3 Effect Modification by ADHD (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 10 Minutes of riding(^1) (duration)</td>
<td>-1.06 (-1.74, -0.40)</td>
<td>-1.18 (-1.90, -0.46)</td>
<td>-0.50 (-1.50, 0.50)</td>
</tr>
<tr>
<td>Per 10 BPM Average HR (intensity)</td>
<td>-0.14 (-0.30, 0.02)</td>
<td>-0.21 (-0.40, -0.02)</td>
<td>-0.31 (-0.65, 0.04)</td>
</tr>
<tr>
<td>Week of Study (time)</td>
<td>--</td>
<td>0.23 (0.06, 0.41)</td>
<td>0.24 (0.07, 0.42)</td>
</tr>
<tr>
<td>Race (Reference: White)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>--</td>
<td>1.88 (-1.30, 5.05)</td>
<td>1.23 (-1.50, 4.95)</td>
</tr>
<tr>
<td>Other</td>
<td>--</td>
<td>-0.79 (-7.81, 6.24)</td>
<td>-0.87 (-8.00, 6.26)</td>
</tr>
<tr>
<td>Male</td>
<td>--</td>
<td>0.66 (-1.77, 3.08)</td>
<td>0.44 (-2.03, 2.91)</td>
</tr>
<tr>
<td>Age</td>
<td>--</td>
<td>-0.48 (-0.98, 0.03)</td>
<td>-0.49 (-0.98, 0.02)</td>
</tr>
<tr>
<td>Has ADHD</td>
<td>--</td>
<td>0.63 (-1.30, 2.55)</td>
<td>0.41 (-6.21, 7.04)</td>
</tr>
<tr>
<td>On Medication</td>
<td>--</td>
<td>-0.22 (-2.02, 1.57)</td>
<td>-0.32 (-2.14, 1.50)</td>
</tr>
<tr>
<td>ADHD*Duration</td>
<td>--</td>
<td>--</td>
<td>-1.37 (-2.76, 0.03)</td>
</tr>
<tr>
<td>ADHD*Intensity</td>
<td>--</td>
<td>--</td>
<td>0.15 (-0.25, 0.55)</td>
</tr>
<tr>
<td>Intercept</td>
<td>11.89 (9.08, 14.70)</td>
<td>16.39 (8.78, 23.99)</td>
<td>17.12 (8.03, 26.21)</td>
</tr>
</tbody>
</table>
### Table 2.2 (continued). Regression modeling results for continuous exercise exposures and measures of behavioral outcomes.

<table>
<thead>
<tr>
<th>Outcome: Minutes of Disciplinary Time Spent Out of Class</th>
<th>β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 10 Minutes of riding (duration)</td>
<td>-8.18 (-13.36, -3.01)</td>
</tr>
<tr>
<td>Per 10 BPM Average HR (intensity)</td>
<td>-1.15 (-2.32, 0.02)</td>
</tr>
<tr>
<td>Week of Study (time)</td>
<td>--</td>
</tr>
<tr>
<td>Race (White=reference)</td>
<td>--</td>
</tr>
<tr>
<td>African American</td>
<td>--</td>
</tr>
<tr>
<td>Other</td>
<td>--</td>
</tr>
<tr>
<td>Male</td>
<td>--</td>
</tr>
<tr>
<td>Age</td>
<td>--</td>
</tr>
<tr>
<td>Has ADHD</td>
<td>--</td>
</tr>
<tr>
<td>On Medication</td>
<td>--</td>
</tr>
<tr>
<td>ADHD*Duration</td>
<td>--</td>
</tr>
<tr>
<td>ADHD*Intensity</td>
<td>--</td>
</tr>
<tr>
<td>Intercept</td>
<td>40.10 (20.92, 59.24)</td>
</tr>
</tbody>
</table>

1No children had zero minutes of riding in PE classes, therefore, duration is rescaled to reflect the minimum riding time of 1.67 minutes.
Effect Modification Modeling

The models showed evidence of effect modification of the association between continuous minutes of riding and both self-regulation score and minutes of disciplinary time out of class by ADHD diagnosis (Table 2.2, Model 3). The main effect of riding duration was no longer significant in either case, but children with ADHD experienced 12.9 minutes (95%CI: -23.5, -2.4) less time out of class and a self-regulation score improvement of 1.4 points (-4.7%, 95%CI: -2.8, 0.0) for each 10 additional minutes of riding. ADHD diagnosis did not appear to modify the relationship between intensity and outcomes. A graphical depiction of the modification of the relationship between exercise duration and outcomes by ADHD diagnosis is shown in Figures 2.1 (TOC) and 2.2 (self-regulation score). Three-way interactions testing differences in exposure-outcome relationships between children with ADHD both taking and not taking medication were not significant in any of the models.
Figure 2.1. Effect modification of the relationship between exercise duration and disciplinary time out of class (TOC) by ADHD status.

Figure 2.2. Effect modification of the relationship between exercise duration and self-regulation score (Conners Abbreviated Teacher Rating Scale – 10 Item) by ADHD status.
Discussion

Few studies to date have examined dose-response relationships between exercise duration and intensity and self-regulation in children. What is more, to our knowledge no studies have been conducted among children with heterogeneous behavioral health disorders in real-world settings. This exploratory follow-up assessment of the Manville Moves RCT showed significant, inverse linear relationships between duration and intensity of cybercycling during PE classes and poor self-regulation scores, and between duration of exercise and minutes of disciplinary time out of class experienced outside of PE classes.

From a clinical standpoint, effects were more pronounced for exercise duration than for intensity. Dose-response models showed that each additional 10 minutes of riding was linked to more than 10 minutes less disciplinary time out of class, and a 3.9% reduction in self-regulation score, an indicator of hyperactivity, impulsivity and emotional lability. It is worth noting again that the amount of time that children spent riding did not affect the amount of time available for them to be asked to leave the academic classroom; children had PE class for the same amount of time regardless of how long they spent riding the cybercycles during that PE class.

Importantly, the effect modification models showed that the main effect of exercise duration on both outcomes was mainly driven by children with ADHD, but this was not the case for intensity. After controlling for medication status, children with ADHD experienced almost 13 minutes less disciplinary time out of class and a 4.7% improvement in self-regulation score for every 10 additional minutes of riding, although the latter was only borderline significant, likely due to a lack of power. That modification was not present for exercise intensity, which
remained borderline significant and strengthened in its association with improved self-regulation scores.

There are a variety of plausible explanations for these effect modification findings. One is that the physiological effects of acute exercise have been shown to influence the same catecholaminergic systems that stimulant medications for ADHD target to improve attention and decrease impulsivity (25). In this study, it appeared that improvements in self-regulation score among children with ADHD were primarily driven by the amount of time that they spent exercising, not the intensity at which they exercised. There are a number of possible explanations for the lack of effect of exercise intensity. It may reflect the low baseline fitness of this population, which might limit variation in intensity more than might be the case in adults or typically developing children. It may also reflect the inherent limitations of using average HR as a measure of intensity. Additionally, we cannot rule out the possibility that it reflects increased measurement error inherent with hand-grip based HR monitoring. Future research seeking to explore these interactions could utilize objective measurement of catecholamine secretion with exercise of differing duration and intensity in children with ADHD in controlled laboratory settings using gold standard intensity measurement instruments.

A limitation of this study is the lack of data on types of medication used, which prevents evaluation of effect modification by medication class. However, children with ADHD diagnoses whose parents reported they were taking medication did not experience different exercise effects when three way interactions were tested. In addition, 72% of children with an ADHD diagnosis in this sample had at least one comorbid behavioral health disorder, and effect modification by differing constellations of diagnoses could not be examined due to small cell sizes. However, while effects of exercise may differ across children with ADHD who also have comorbidities,
we show that the common diagnosis of ADHD is a significant effect modifier of outcomes, despite any such variation. Future research should focus on quantifying effects of aerobic exercise duration in combination with differing doses of stimulant medication in children with ADHD, in order to understand the feasibility and limitations of using exercise as a primary therapeutic approach for managing ADHD symptoms.

This study takes important first steps in identifying potential dose-response relationships between exercise duration and intensity and behavioral health outcomes in children with behavioral health disorders. Our findings indicate that aerobic exercise of even relatively short duration and moderate intensity is likely behaviorally beneficial to children with a variety of behavioral health disorders, and that there is a particularly a strong positive dose-response relationship between duration of aerobic exercise and self-regulation and classroom functioning among children with ADHD.

**Acknowledgements**

The authors would like to thank the students, families, and staff at the Manville School for their participation in the implementation and evaluation of *Manville Moves*, in particular Brian Wood, Bobby Hermesch, Jim Prince, and Amanda Hayes. We would also like to thank Tom McCarthy for providing equipment technical support and expertise, as well as Richard Kow, Sami Newlan, and Jeanette Garcia for their assistance with the data collection and review process. This study was supported by a private grant to Harvard T.H. Chan School of Public Health.
Conflict of interest

The authors declare that they have no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

References


Chapter 3:
ADHD Medication, Dietary Patterns, Physical Activity, and BMI in Children:
A Longitudinal Analysis of the ECLS-K Study

April Bowling, Kirsten Davison, Sebastien Haneuse, William Beardslee, Daniel P. Miller
Abstract

Purpose: We examined relationships between ADHD, stimulant use and BMI change in a nationally-representative cohort of children, as well as differences in diet/physical activity that may mediate associations between stimulant use and BMI change.

Methods: Using the Early Childhood Longitudinal Study-Kindergarten cohort 1998-1999 (N=8250), we modeled BMI/z-score change by ADHD and stimulant start time, odds of unhealthy diet/physical activity predicted by ADHD and stimulant use, and performed mediation analysis assessing indirect effects of health behaviors.

Results: Early stimulant use predicted short-term BMI reductions, but any stimulant use predicted increased BMI growth between 5th and 8th grade. Children with ADHD had higher odds of poor diet regardless of medication. Health behaviors did not mediate associations between stimulants and BMI change.

Conclusions: Stimulant use predicted higher BMI trajectory between 5th and 8th grade but not improved health behaviors. Future research should explore potential mechanisms by which early/long-term stimulant use may affect metabolism.
Background and Rationale

The Centers for Disease Control and Prevention estimates that about 5.1 million children were diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD) in 2011, representing about 9% of all children between the ages of 4 and 17 in the United States (Visser et al., 2014). Of those diagnosed, approximately 3.5 million (69%) were taking at least one medication, usually a stimulant, intended to treat ADHD symptoms (Visser et al., 2014). Stimulant use is greatest between 6 and 12 years of age, although use among adolescents is increasing at the highest rate (Zuvekas & Vitiello, 2012).

A recent meta-analysis of 42 studies conducted by Cortese et al. (Cortese et al., 2015) found that children ages 6 to 17 who were reported as having an ADHD diagnosis had 1.20 times the odds of obesity (95% CI: 1.05-1.37) as those without the disorder, while adults with ADHD had 1.55 times the odds (95% CI: 1.32-1.81). Several mechanisms have been identified that may explain this association. Firstly, ADHD is highly comorbid with conditions that may be independently associated with weight gain including depression, anxiety, substance abuse, conduct disorder, and oppositional defiant disorder (Larson, Russ, Kahn, & Halfon, 2011; Pauli-Pott, Neidhard, Heinzl-Gutenbrunner, & Becker, 2014). Secondly, the impulsivity aspect and brain chemistry pathology of ADHD are hypothesized to combine to contribute to disordered eating patterns, including binge eating and food addiction (Cortese & Morcillo, 2010; Davis, Levitan, Smith, Tweed, & Curtis, 2006). Finally, genetic and fetal programming may contribute to underlying biological mechanisms that drive both ADHD development and metabolic dysregulation (Rodriguez et al., 2008), and a bidirectional association has been suggested via neurotransmitter and endocrine changes associated with increased adiposity (Cortese & Morcillo, 2010).
Until recently, however, stimulant medication treatment of ADHD was not considered as a potential contributory factor to increased overweight and obesity risk among children with ADHD. This was because only cross-sectional and short-term longitudinal studies of 3 months to three years had been conducted. These studies either found no association, or found that short-term stimulant use was associated with growth deficits and lower body mass index (BMI) (Charach, Figueroa, Chen, Ickowicz, & Schachar, 2006; Spencer, Biederman, & Wilens, 1998; Zachor, Roberts, Hodgens, Isaacs, & Merrick, 2006), likely varying by developmental period and due to short-term endocrine and anorexigenic side effects of stimulants (Leonard, McCartan, White, & King, 2004).

Cortese et al.’s meta-analysis pooled results from 12 such studies of obesity risk in both medicated and unmedicated children, adolescents and adults with ADHD, and found no evidence that individuals with medicated ADHD were at increased risk of obesity (odds ratio 1.00, 95%CI: 0.87-1.15), but higher odds of obesity for those with unmedicated ADHD (odds ratio=1.43, 95% CI: 1.23-1.67) (Cortese et al., 2015). However, of the 11 studies conducted in children and/or adolescents, 10 were cross-sectional, and none stratified point estimates of associations between BMI and medication status by duration of medication use to examine associations between stimulant use and obesity risk after the initial weight loss and growth retardation period of 1 to 3 years (Cortese et al., 2015). Also, none of the studies looked at differences in associations by developmental periods, which could be critical, since some studies have shown that children with ADHD exhibit delayed physical maturation independent of medication status, perhaps due to ADHD’s association with low birthweight (Van Mil et al., 2015).
The only long-term, prospective longitudinal study examining BMI trajectory differences by stimulant use and duration was not included in Cortese et al.’s meta-analysis (Schwartz et al., 2014). The Schwartz study used longitudinal electronic health record data from Pennsylvania’s Geisinger Health System on 163,820 children ages 3 to 18 years, and modeled BMI trajectories with increasing age in relation to ADHD diagnosis, age at first stimulant use, and stimulant use duration. It found associations between early and long-term stimulant use in childhood and subsequent increased BMI trajectory into overweight and obesity in adolescence and early adulthood, but did not find such an association in individuals with unmedicated ADHD (Schwartz, Bailey-Davis et al. 2014).

While this study design was rigorous and advanced understanding of the complex relationships between ADHD diagnosis, stimulant use, and obesity, the study population was primarily white and higher income, and a similar exploration has not been made to date in a more nationally representative sample with racial/ethnic, socioeconomic, and geographic diversity. Importantly, the Schwartz study also left open the question of mechanisms; thus even if the results are replicable it is unclear if the positive relationship between long-term stimulant use and increase in BMI trajectory occurs because of differences in health behaviors such as dietary intake and physical activity among children taking medication. A conceptual model of these relationships is shown in Figure 3.1.
In order to help address these gaps in our understanding, this study will use the Early Childhood Longitudinal Study 1998-99 Kindergarten Cohort (ECLS-K98) dataset to investigate two primary aims. First, we will examine whether the positive association between long-term ADHD medication use and increased BMI trajectory during early adolescence found by Schwartz et al. is evident in a nationally representative sample of children, and if such a relationship changes by developmental stage or becomes more pronounced with longer durations of reported use (Aim 1). Secondly, we will examine differences in 5th grade dietary patterns and physical activity levels between children without ADHD, those with unmedicated ADHD, and those with medicated ADHD, and test whether any relationship between long-term stimulant use and increases in BMI and BMI z-score between 5th and 8th grade are mediated by parent-reported physical activity levels and child-reported unhealthy diet score (Aim 2).
Methods

Study Design

This study uses data from the ECLS-K98, a prospective observational cohort of kindergarteners and their parents, teachers, and schools that began in 1998-1999, and was conducted by the National Center for Education. Data collection occurred in kindergarten, 1st grade, 3rd grade, 5th grade, and 8th grade (5 waves). Including the base year and sample refreshing in 1st grade, 21,410 children were enrolled and 9,360 had data collected on them through 8th grade. Much of the decrease in sample size is a consequence of planned attrition, as the ECLS-K98 only followed children who remained in their initial school, as well as a small subsample of children who switched schools during the study period.

We used multiple imputation with chained equations to account for missing values in covariates, accommodating arbitrary missing value patterns (White, Royston, & Wood, 2011). Imputations were based on available information on all variables included in the study, as well as additional baseline demographic variables. Following recommendations in the literature on multiple imputation, this study excludes children for whom BMI was not collected in 5th or 8th grade (Von Hippel, 2007), as well as those starting stimulants between 5th and 8th grade since the exposure would not temporally precede the outcome, for a final complete case study population of N=8,250.

Measures:

ADHD Diagnosis and Medication Use: In each wave, parents were asked if their child had received a diagnosis of ADHD by a health care professional. In the 5th and 8th grade waves, all

\[\text{All sample sizes have been rounded to the nearest 10 to comply with ECLS-K98 reporting and privacy requirements.}\]
parents who reported a diagnosis of ADHD for their child in the current or previous waves were asked the question, “Is your child now taking any prescription medicine for the condition related to his or her ADD, ADHD, or hyperactivity?” If they reported medication use, they were then asked regarding the duration of use (less than 1 year, 1-2 years, 3-4 years, 5 or more years), and the name of the medication. Those answers were used to code dummy variables representing whether children began a stimulant medication prior to 1st grade, between 1st grade and 3rd grade, or between 3rd grade and 5th grade.

**BMI and BMI z-score:** Trained ECLS-K98 staff members measured children's height and weight in the spring of each data collection wave using a Shorr board (accuracy: 0.01 cm) and a Seca digital bathroom scale (model 840 [Seca, Hanover, MD]; accuracy: 0.1 kg), respectively. Children were asked to remove shoes and heavy clothing prior to measurement. Height and weight were measured two times consecutively in order to minimize errors, and averaged when the discrepancy between replicates was less than 5.1 cm for height and 2.27 kg for weight (98% of cases); otherwise, the value closest to the grade-level median was used (Tourangeau, Nord, Lê, Sorongon, & Najarian, 2009). BMI was calculated using weight in kilograms divided by the square of height in meters (kg/m²). BMI z-scores were then calculated using CDC 2000 Growth Reference standards for age and gender.

**Health Behaviors:** Health behavior questions on the ECLS-K98 were mainly taken from two existing surveys conducted by the Centers for Disease Control and Prevention (CDC)/Division of Adolescent and School Health Surveys: the Youth Risk Behavior Surveillance Survey (YRBSS) and the School Health Programs and Policies Survey (SHPPS) (Tourangeau et al., 2009). One food consumption question on fast-food meals was taken from the California Children’s Healthy Eating and Exercise Practices Survey (CalCheeps) (Tourangeau et al., 2009).
Physical activity was operationalized as parent-reported number of days per week where the child experienced 20 or more consecutive minutes of moderate to vigorous intensity exercise. Diet score is generated as a summary measure of 6 questions on dietary intake asked of students in 5th and 8th grades. These questions (3 on vegetable and salad intake, 2 on sugar sweetened beverage (SSB) intake, 1 on fast food intake) were used to construct an “unhealthy diet pattern” score. Children reporting less than one serving of salad or vegetables per day, those reporting more than 1 SSB serving per day, and those eating fast food more than 3 times per week all received 1 point each, for a possible score ranging from 0 (most healthy) to 3 (most unhealthy).

Covariates: Covariates included parent-reported child characteristics of age, race/ethnicity, sex, socioeconomic status (SES), and comorbid behavioral health diagnoses, as well as teacher-reported externalizing symptoms in kindergarten as measured by the externalizing sub-scale of the Child Behavior Checklist (CBCL) (Ebesutani et al., 2010). The components used to create the continuous SES variable are father/male guardian’s education, mother/female guardian’s education, father/male guardian’s occupational prestige, mother/female guardian’s occupational prestige, and household income. In households with two mothers or two fathers, education and occupational prestige for both mothers/fathers was used. Each parent’s occupation was scored using the average of the 1989 General Social Survey (GSS) prestige scores for the 1980 census occupational category codes that correspond to the ECLS-K98 occupation code. The demographic covariates were collected from parents during baseline interviews, while data on parental report of comorbid diagnoses was obtained at each wave.
Statistical Analyses

All analyses were conducted using STATA 13. ANOVA and chi-square tests were used to evaluate differences in demographic variables among the three groups of interest (children without ADHD, those with unmedicated ADHD, those with ADHD medicated by 5\textsuperscript{th} grade). For Aim 1, we used multiple linear regression to first model BMI change by developmental period (1\textsuperscript{st} to 3\textsuperscript{rd} grade, 3\textsuperscript{rd} to 5\textsuperscript{th} grade, and 5\textsuperscript{th} and 8\textsuperscript{th} grade) using dummy variables representing medication start time (before 1\textsuperscript{st} grade, between 1\textsuperscript{st} and 3\textsuperscript{rd} grade, and between 3\textsuperscript{rd} and 5\textsuperscript{th} grade) as the outcome predictor. We then adjusted the models to control for baseline confounders identified in the literature and conceptual modeling including race/ethnicity, socioeconomic status, sex, birthweight, comorbid behavioral health diagnoses, and teacher reported externalizing behavior at baseline (Cortese & Morcillo, 2010; van Egmond-Fröhlich, Widhalm, & De Zwaan, 2012; Van Mil et al., 2015). We then replicated both the unadjusted and confounder adjusted models using change in BMI z-score, which provides age and gender standardized context for effect size and may aid clinical interpretability. Finally, we tested equality of coefficients to evaluate if BMI effects differed significantly for the various medication start times.

For Aim 2, we dichotomized dietary scores and physical activity levels and used logistic regression to model the odds of unhealthy behaviors (unhealthy diet score ≥ 2 and physical activity level < 3 days per week) as predicted by ADHD diagnosis and medication category, in both unadjusted and confounder adjusted models (Howard et al., 2011). Finally, we conducted a mediation analysis utilizing both Sobel-Goodman tests and calculation of indirect effects post-imputation (Baron & Kenney 1986, Hayes 2013) to determine if physical activity levels or diet scores are significant mediators of any effects of medication on BMI change.
Results

Table 3.1 shows baseline characteristics of the children in the study sample (n=8250), and differences across the groups of interest. Parents reported a diagnosis of ADHD by a health care provider for approximately 8% of the children in the sample (n=650). Among children diagnosed with ADHD by 5th grade, almost 60% were taking medications to manage symptoms (n=380). Children taking medication were more likely to be white (p=0.03) than children with ADHD who remained unmedicated by the 5th grade. Of children who were medicated, 60 were taking medication by 1st grade, 120 were reported as having started medication between 1st and 3rd grade, and 190 were reported as starting between 3rd and 5th grade. Bivariate results suggest that mean BMI was not different between children without ADHD and those with unmedicated ADHD in 5th grade, however, it was significantly lower for children with medicated ADHD (p<0.001). By 8th grade, no significant difference among the three groups remained.
### Table 3.1. Characteristics of the study population.

<table>
<thead>
<tr>
<th>Child Characteristics</th>
<th>Total Sample N=8250</th>
<th>No ADHD n=7600</th>
<th>Unmedicated ADHD n=270</th>
<th>Medicated ADHD n=380</th>
<th>Test Statistic$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M) (%)</td>
<td>49.9</td>
<td>48.0</td>
<td>70.4</td>
<td>73.7</td>
<td>$\chi^2=138.2$, p&lt;0.001</td>
</tr>
<tr>
<td>Mean age at start of 5th grade (years)</td>
<td>11.2±.4</td>
<td>11.2±.4</td>
<td>11.2±.4</td>
<td>11.3±.4</td>
<td>F=1.17, p=0.31</td>
</tr>
<tr>
<td>Mean BMI in 5th grade (kg/m$^2$)</td>
<td>20.5±4.7</td>
<td>20.6±4.7</td>
<td>20.2±4.6</td>
<td>19.1±4.3</td>
<td>F=20.2, p&lt;0.001</td>
</tr>
<tr>
<td>Mean BMI in 8th grade (kg/m$^2$)</td>
<td>22.8±5.4</td>
<td>22.9±5.4</td>
<td>22.6±5.3</td>
<td>22.3±5.1</td>
<td>F=2.3, p=0.11</td>
</tr>
<tr>
<td>Mean BMI change from 5th to 8th grade (kg/m$^2$)</td>
<td>2.3±2.8</td>
<td>2.3±2.8</td>
<td>2.4±2.6</td>
<td>3.2±2.4</td>
<td>F=23.2, p&lt;0.001</td>
</tr>
<tr>
<td>Mean BMI z-score change 5th to 8th grade</td>
<td>-0.01±0.58</td>
<td>-0.02±0.57</td>
<td>0.00±0.61</td>
<td>0.29±0.67</td>
<td>F=55.3, p&lt;0.001</td>
</tr>
<tr>
<td>Physical activity level (days/week)</td>
<td>3.7±1.9</td>
<td>3.7±1.8</td>
<td>3.8±2.0</td>
<td>3.6±2.0</td>
<td>F=0.83, p=0.44</td>
</tr>
<tr>
<td>Unhealthy diet score$^a$</td>
<td>0.93±0.81</td>
<td>0.90±0.81</td>
<td>1.23±0.82</td>
<td>1.20±0.82</td>
<td>F=43.64, p&lt;0.001</td>
</tr>
<tr>
<td>Early externalizing symptoms$^b$</td>
<td>1.6±0.6</td>
<td>1.6±0.6</td>
<td>2.0±0.8</td>
<td>2.2±0.7</td>
<td>F=245.9, p&lt;0.001</td>
</tr>
<tr>
<td>Comorbid behavioral health diagnosis (%)</td>
<td>3.2</td>
<td>2.0</td>
<td>11.1</td>
<td>21.1</td>
<td>$\chi^2=495.2$, p&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3.1 (continued). Characteristics of the study population.\textsuperscript{1}

<table>
<thead>
<tr>
<th>Family Characteristics</th>
<th>SES\textsuperscript{c} (%)</th>
<th>\chi^2=13.8, p=0.09</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quintile 1</td>
<td>Quintile 2</td>
</tr>
<tr>
<td>SES\textsuperscript{c} (%)</td>
<td>14.5</td>
<td>14.6</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>17.1</td>
<td>16.8</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>19.2</td>
<td>18.9</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>21.6</td>
<td>21.7</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>24.5</td>
<td>24.6</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>10.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Asian</td>
<td>5.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17.1</td>
<td>17.8</td>
</tr>
<tr>
<td>White</td>
<td>61.9</td>
<td>60.8</td>
</tr>
<tr>
<td>Other</td>
<td>5.0</td>
<td>5.1</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Descriptive statistics are for observed data (unimputed); some observations were missing data so sample sizes varied for physical activity (n=7810), diet (n=7910), externalizing symptoms (n=7810), comorbid diagnoses (n=7930), and SES (n=7980). Sample sizes for all descriptive statistics are rounded to the nearest 10 before conversion to percentages to comply with National Center for Education’s privacy requirements. Therefore, not all categories will add to 100%.

\textsuperscript{2}Degrees of freedom are redacted as required by the National Center of Education’s privacy requirements.

\textsuperscript{a}Out of a possible 3 points (0=most healthy, 3=most unhealthy).

\textsuperscript{b}On a 1-4 point Likert Scale.

\textsuperscript{c}SES quintiles as calculated by the National Center for Education Statistics from the full ECLS-K98 sample at baseline.
**Aim 1:** Modeling results of medication start time as the predictor of BMI and z-score change are shown in Table 3.2. In both unadjusted and confounder adjusted models, unmedicated ADHD was negatively associated with BMI change up to 3rd grade, after which the association became non-significant. In the unadjusted model, starting medication before 1st grade was negatively associated with BMI change from 1st to 3rd grade, not significantly associated with BMI change from 3rd to 5th grade, and positively associated with change from 5th to 8th grade. Once the model was adjusted for confounders, starting medication by 1st grade remained inversely associated with BMI change through 5th grade, and still became positively associated with increased BMI change from 5th to 8th grade. Both models found that starting medication between 1st and 3rd grade was not significantly associated with BMI change from 3rd to 5th grade, but was associated with a nearly 1.2 kg/m² greater increase in BMI change from 5th to 8th grade. Finally, beginning medication between 3rd and 5th grade was positively associated with BMI increases from 5th to 8th grade in both unadjusted and adjusted models. For all three medication start times, this association translates to about a 0.3 SD increase in children’s BMI z-score from 5th to 8th grade, while children with unmedicated ADHD experience the same rate of growth as those without an ADHD diagnosis. Tests of the equality of coefficients showed no significant difference among the increased BMI and BMI z-score changes from 5th to 8th grade experienced by children with different medication start times.
### Table 3.2. Linear regression modeling results for BMI and BMI z-score outcomes.

<table>
<thead>
<tr>
<th></th>
<th>ΔBMI 1&lt;sup&gt;st&lt;/sup&gt;-3&lt;sup&gt;rd&lt;/sup&gt; Grade</th>
<th>ΔBMI 3&lt;sup&gt;rd&lt;/sup&gt;-5&lt;sup&gt;th&lt;/sup&gt; Grade</th>
<th>ΔBMI 5&lt;sup&gt;th&lt;/sup&gt;-8&lt;sup&gt;th&lt;/sup&gt; Grade</th>
<th>ΔzBMI 1&lt;sup&gt;st&lt;/sup&gt;-3&lt;sup&gt;rd&lt;/sup&gt; Grade</th>
<th>ΔzBMI 3&lt;sup&gt;rd&lt;/sup&gt;-5&lt;sup&gt;th&lt;/sup&gt; Grade</th>
<th>ΔzBMI 5&lt;sup&gt;th&lt;/sup&gt;-8&lt;sup&gt;th&lt;/sup&gt; Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1: Unadjusted&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmedicated before 5&lt;sup&gt;th&lt;/sup&gt; grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-0.37</td>
<td>0.22</td>
<td>0.13</td>
<td>-0.02</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>(−0.67, −0.07)</td>
<td>(−0.02, 0.47)</td>
<td>(−0.21, 0.48)</td>
<td></td>
<td>(−0.12, 0.09)</td>
<td>(−0.00, 0.13)</td>
<td>(−0.05, 0.09)</td>
</tr>
<tr>
<td>Starting Medication by 1&lt;sup&gt;st&lt;/sup&gt; Grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-1.28</td>
<td>-0.41</td>
<td>1.02</td>
<td>-0.38</td>
<td>-0.03</td>
<td>0.33</td>
</tr>
<tr>
<td>(−1.88, −0.69)</td>
<td>(−0.90, 0.07)</td>
<td>(0.34, 1.70)</td>
<td></td>
<td>(−0.59, −0.17)</td>
<td>(−0.16, 0.10)</td>
<td>(0.18, 0.47)</td>
</tr>
<tr>
<td>Starting Medication between 1&lt;sup&gt;st&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; Grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>--</td>
<td>-0.26</td>
<td>1.17</td>
<td>--</td>
<td>-0.00</td>
<td>0.36</td>
</tr>
<tr>
<td>(−0.61, 0.09)</td>
<td>(0.68, 1.66)</td>
<td></td>
<td></td>
<td>(−0.10, 0.09)</td>
<td>(0.26, 0.46)</td>
<td></td>
</tr>
<tr>
<td>Starting Medication between 3&lt;sup&gt;rd&lt;/sup&gt; and 5&lt;sup&gt;th&lt;/sup&gt; Grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>0.83</td>
<td>--</td>
<td>--</td>
<td>0.28</td>
</tr>
<tr>
<td>(0.44, 1.22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.20, 0.36)</td>
<td></td>
</tr>
<tr>
<td><strong>Model 2: Confounder adjusted&lt;sup&gt;1,3&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmedicated before 5&lt;sup&gt;th&lt;/sup&gt; grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-0.43</td>
<td>0.13</td>
<td>0.07</td>
<td>-0.04</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>(−0.73, −0.13)</td>
<td>(−0.12, 0.38)</td>
<td>(−0.28, 0.41)</td>
<td></td>
<td>(−0.14, 0.07)</td>
<td>(−0.00, 0.14)</td>
<td>(−0.07, 0.08)</td>
</tr>
<tr>
<td>Starting Medication by 1&lt;sup&gt;st&lt;/sup&gt; Grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-1.30</td>
<td>-0.50</td>
<td>0.94</td>
<td>-0.42</td>
<td>-0.05</td>
<td>0.30</td>
</tr>
<tr>
<td>(−1.90, −0.71)</td>
<td>(−0.99, −0.01)</td>
<td>(0.25, 1.62)</td>
<td></td>
<td>(−0.64, −0.20)</td>
<td>(−0.19, 0.09)</td>
<td>(0.16, 0.44)</td>
</tr>
<tr>
<td>Starting Medication between 1&lt;sup&gt;st&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; Grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>--</td>
<td>-0.29</td>
<td>1.19</td>
<td>--</td>
<td>-0.03</td>
<td>0.35</td>
</tr>
<tr>
<td>(−0.64, 0.07)</td>
<td>(0.70, 1.68)</td>
<td></td>
<td></td>
<td>(−0.13, 0.07)</td>
<td>(0.25, 0.45)</td>
<td></td>
</tr>
<tr>
<td>Starting Medication between 3&lt;sup&gt;rd&lt;/sup&gt; and 5&lt;sup&gt;th&lt;/sup&gt; Grade&lt;sup&gt;2&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
<td>0.78</td>
<td>--</td>
<td>--</td>
<td>0.27</td>
</tr>
<tr>
<td>(0.39, 1.18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.18, 0.35)</td>
</tr>
</tbody>
</table>

<sup>1</sup>The reference group is children without ADHD.

<sup>2</sup>Children in both unmedicated and medicated categories have been reported as diagnosed with ADHD by a healthcare provider.

<sup>3</sup>BMI change model is adjusted for socioeconomic status (SES), race/ethnicity, sex, age, comorbid behavioral health diagnoses, birth weight, and externalizing symptoms in 1<sup>st</sup> grade; z-score model is adjusted for SES, race/ethnicity, comorbid behavioral health diagnoses, birth weight, and externalizing symptoms in 1<sup>st</sup> grade as z-scores are standardized for age and sex.
**Aim 2:** Logistic modeling results for the dichotomous outcomes of unhealthy physical activity levels and dietary scores are shown in Table 3.3. The adjusted model showed that the odds of having low levels of parent-reported physical activity levels in 5th grade were significantly higher for children who had ADHD and were medicated by 5th grade (adjusted OR=1.27, 95% CI: 1.02, 1.59) relative to children without ADHD; this was not the case for children with unmedicated ADHD (OR=1.02, 95% CI: 0.79, 1.32). In the both the unadjusted and confounder adjusted models, odds of having an unhealthy diet score were higher for children with ADHD, regardless of whether they were medicated (adjusted OR= 2.17, 95% CI: 1.39-3.38) or not (adjusted OR=1.88, 95% CI: 1.13, 3.10).

**Table 3.3.** Logistic regression results for dietary patterns and physical activity outcomes in 5th grade.

<table>
<thead>
<tr>
<th></th>
<th>Unhealthy Physical Activity Level (Days per week&lt;3)</th>
<th>Unhealthy Dietary Pattern (Score≥2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Model 1: Unadjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not medicated (ADHD diagnosis)</td>
<td>0.90 (0.70, 1.16)</td>
<td>1.81 (1.39, 2.36)</td>
</tr>
<tr>
<td>Medicated (ADHD diagnosis)</td>
<td>1.08 (0.88, 1.33)</td>
<td>1.62 (1.29, 2.02)</td>
</tr>
<tr>
<td><strong>Model 2: Confounder adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not medicated (ADHD diagnosis)</td>
<td>1.02 (0.79, 1.32)</td>
<td>1.52 (1.15, 2.00)</td>
</tr>
<tr>
<td>Medicated (ADHD diagnosis)</td>
<td>1.27 (1.02, 1.59)</td>
<td>1.41 (1.11, 1.81)</td>
</tr>
</tbody>
</table>

1 Reference category is children without ADHD.
2 Adjusted for SES, race/ethnicity, sex, comorbid behavioral health diagnoses, and externalizing symptoms in 1st grade.
Both Sobel-Goodman tests and calculation of indirect effects post-imputation found no significant mediation of the relationship between BMI change between 5th and 8th grade and medication use by either child-reported diet score or parent-reported physical activity level in 5th grade. The indirect effect of medication use through diet was very small (β=0.01, 95% CI: -0.01, 0.03), representing only 1.2% of the total effect of medication use on BMI change. The indirect effect of medication use through physical activity was also negligible (β= -0.01, 95% CI: -0.02, 0.00) at 0.8% of the total effect.

Discussion

Mean BMI in 5th grade was significantly lower among children taking medication to manage their ADHD symptoms as compared to children who were not taking medication. Although this cross-sectional finding cannot be causally interpreted, it was expected given the evidence that stimulant use can reduce growth rates for up to two to three years in young children and the median medication start time for the sample was 3rd grade (Charach et al., 2006). However, these children experienced greater increases in BMI between 5th and 8th grade; thus by 8th grade their mean BMI was no longer significantly different from either typically developing children, or those with ADHD who remained unmedicated. While early medication use prior to 3rd grade appears to predict greater BMI increases between 5th and 8th grade, this predicted increase was not significantly different from that associated with a later start time. Children with unmedicated ADHD did not experience either higher BMI or greater BMI change during any developmental period. This was the case whether we controlled for early externalizing symptom severity or not, which demonstrates the associations are unlikely to be confounded by indication.

When viewed in context with previous studies, our findings appear very consistent with Schwartz et al.’s results, and provide further insight among a geographically and
demographically diverse sample. Certainly, our study provides additional evidence of BMI rebound during pre- and early adolescence among children who have ADHD and begin stimulant use before 5th grade. By contrast, after controlling for confounders and medication use, we found a negative association between unmedicated ADHD diagnosis and BMI increases up to 3rd grade, and no association after that time. While this appears to conflict with the findings of the Cortese et al. meta-analysis, it is likely due to the fact that the meta-analysis relied on cross-sectional data in medicated children with ADHD, and could not distinguish between developmental periods or short- versus long-term medication use. However, we did find that children with ADHD diagnoses have worse diet scores regardless of medication use, and there is an indication of slightly increased BMI trajectory (non-significant) among these children between 5th and 8th grade, which may not manifest in significant differences until later in the life course.

While there was an increased risk of low physical activity levels among children taking medication, neither physical activity levels nor dietary score acted as mediators of the relationship between medication use and BMI change. This may provide some evidence that the positive association between increased BMI trajectory and long-term stimulant use could be due not to differences in health behaviors among children with medicated and unmedicated ADHD, but instead to physiological changes or metabolic compensation associated with early and long-term use of stimulants.

Unfortunately, this analysis is limited by the lack of follow-up after 8th grade; thus we cannot confirm that these BMI trajectories are maintained after the study period, and so we cannot determine from this data whether the increased BMI gains among stimulant medicated children simply represent growth catch up after initial stimulant use, or as Schwartz et al. found, predicate a continued increased trajectory into higher risk of overweight and obesity (Schwartz et al., 2014).
However, it is important to note that no studies have found large changes in established population level BMI trajectory after 8th grade (Williams & Goulding, 2009).

Though we used multiple imputation to account for missing data, we dropped cases where data was missing on the dependent variables. Therefore, the significant attrition in the study means that children with more severe ADHD symptoms may be disproportionately lost to follow up, which may influence the finding of no association between unmedicated ADHD and BMI increases. However, this possibility is made less likely because there were no significant differences between the proportion of overall attrition and attrition by children with diagnosed ADHD, as well as no differences in externalizing symptoms between those leaving the study and those remaining.

Finally, physical activity and diet are not objectively measured, which increases measurement error, decreases the likelihood of detecting differences among the groups, and increases the likelihood that that the indirect effect is attenuated in mediation analyses (Baron & Kenny, 1986). However, the very small indirect effects indicates that while future research should focus on objectively measuring health behaviors and clarifying these relationships during later adolescence, it is critical to develop a better evidence base regarding potential physiologic mechanisms by which stimulants may affect long-term metabolism. Also, given that children with ADHD were found to have significantly worse diets despite measurement limitations and regardless of medication status, this finding should be taken seriously.

Associations between ADHD diagnosis, stimulant medication use and BMI changes have important clinical implications. Longitudinal evidence of higher pre- and early adolescent BMI trajectory among children using stimulant medications in childhood may simply reflect growth catch-up, but it may also indicate that metabolic compensation is occurring associated with early
and extended stimulant use. These weight gain impacts may only be exacerbated if children are co-
pharmacologically treated with second generation antipsychotics, which are increasing in pediatric
use and known to causally increase adiposity (Penzner et al., 2009).

Given the longitudinal evidence, stimulants should not be viewed by physicians as a tool to
reduce obesity risk among children with ADHD, at least until additional research is conducted. By
the same token, there is not enough evidence to suggest that future obesity risk should deter
prescriptions indicated to treat ADHD’s behavioral symptoms. Since children with ADHD do
appear to be at higher risk of poor dietary intake, clinicians should consider lifestyle counseling
following an ADHD diagnosis regardless of medication prescription.

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