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Predictors of Changes in Height, Weight, and Body Mass Index after Initiation of Central Nervous System Stimulants in Children with Attention-Deficit/Hyperactivity Disorder

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Data sharing: Deidentified data will be made available that underlie results in this article from 6 to 36 months after publication for individual participant data meta-analysis for investigators who provide a methodologically sound proposal by emailing jwaxmonsky@pennstatehealth.psu.edu.

Keywords: ADHD, growth, CNS stimulants, children, weight loss

Abbreviations

ADHD (Attention Deficit Hyperactivity Disorder); CNS (Central Nervous System); BMI (Body Mass Index); WRT (Weight Recovery Treatment); MG (Milligrams); MTA (Multimodal Treatment of ADHD Study); CM centimeters; KG kilograms

Objective: To identify predictors of changes in height, weight, and BMI in children with ADHD starting Central Nervous System (CNS) stimulants. **Study design:** 230 medication-naïve children ages 5-12 with ADHD participated in a randomized trial evaluating the impact of CNS stimulants on growth over 30 months. This observational analysis focused on the 141 participants using study medication for $\geq 50\%$ of weekdays over any 6-month period. Biometric variables, ADHD and oppositional defiant disorder symptom scores at medication initiation and medication usage over the study were examined as predictors of changes in standardized height,

weight, and BMI. **Results:** Mean changes in z-BMI, z-weight and z-height were negative throughout the study. The most consistent predictors of change in z-BMI, z-weight and z-height were percent days medicated and total medication exposure. Children with lower z-height and z-weight at medication initiation experienced greater z-BMI and z-weight reductions over the first 6 months on medication. Greater appetite suppression during dose optimization predicted greater reductions in z-weight over the entire study and greater reduction in z-height over the first 6 months on medication. Weight change correlated with height change. Behavioral symptoms did not predict changes in z-BMI, z-weight or z-height. **Conclusions:** How much and how often CNS stimulants are used predicts changes in z-BMI, z-weight, and z-height in children. Even smaller and lighter children may be at risk for z-weight and z-BMI decline. Parent ratings of appetite during dose titration may serve as feasible indicators of future weight and height change in children using CNS stimulants.

Trial registration Clinicialtrials.gov: NCT01109849

Central nervous system (CNS) stimulants are one of the most commonly prescribed pediatric medications.¹⁻⁴ Side effects are a frequent reason parents are hesitant to use CNS stimulants and why patients discontinue them.^{5, 6 7, 8} Anorexia and weight loss are often seen with CNS stimulants⁹⁻¹¹ and can lead to treatment discontinuation.^{1, 12} CNS stimulants are associated with a standard mean difference of 0.27 for height and 0.33 for weight. The largest impact on weight occurs during the first 6 months and height by months 24-30.¹³ The National Institute of Mental Health Multimodal Treatment of ADHD (MTA) study observed the most growth suppression in youth medicated prior to enrollment who consistently used medication over the next decade. The greatest slowing in height velocity occurred in the first two years of use.¹⁴ Growth velocity did not meaningfully rebound while taking CNS stimulants, suggesting that “catch-up” growth does not occur if medication is continued.^{15, 16}

Identifying reliable indicators of weight loss and growth suppression could aid detection of children at greatest risk for clinically impactful decelerations with CNS stimulants and reassure families of children without identified risk factors. Weight and height deficits are correlated in some studies,¹⁷⁻¹⁹ suggesting that initial weight loss could predict growth. Results about the impact of dose and age are mixed.^{13, 14, 17} . Besides the MTA, there has been limited examination of the impact of duration of exposure on growth. Some studies observed that premedication height and weight were inversely correlated with future suppression, leading a widely cited review on this topic to conclude that shorter or lighter youth are at lower risk for medication associated decelerations of height or weight velocity.^{17, 20, 21} One study observed that extended treatment with CNS stimulants led to a doubling in the percentage of children below 1.5 standard deviations for z-height, suggesting that shorter youth may develop meaningful suppression with CNS stimulants.²²

Few treatment studies of ADHD were designed to measure growth, and most studies did not measure height at recurring intervals using standardized procedures.²³ Additional limitations included not assessing pubertal status, short study duration, limited documentation of medication use and use of immediate release CNS stimulants which have been increasingly replaced by extended release (ER) versions.^{13, 17} The growth trajectories of 230 treatment naïve youth randomly assigned to behavior therapy or ER CNS stimulants were prospectively tracked over 30 months and the impact of caloric supplementation, drug holidays and increased monitoring on height, weight and body mass index (BMI) trajectory were assessed.²⁴ This observational analysis examines predictors of standardized BMI, height and weight change for all participants recurrently using CNS stimulant medication in that study. The greatest declines in weight and height were hypothesized to occur in participants with the highest standardized height and weight scores at baseline, the largest exposure to study medication and for weight and BMI, the highest level of parent rated changes in appetite.

Methods

The funded study was designed to assess height and weight trajectories of children with ADHD using CNS stimulants and the effects of weight recovery treatments (WRT) on their growth.²⁴ Participants were 230 children ages 5 to 12 meeting criteria for any Diagnostic and Statistical Manual of Mental Disorders(DSM)-IV ADHD subtype. Exclusion criteria were IQ < 70, BMI below the 5th percentile or above the 94th, use of CNS stimulants for over 30 days before enrollment, use of other psychotropics or medications that impair growth (eg, systemic oral steroids), autism spectrum disorder or medical contraindications to CNS stimulants. Consistent with the local area, 73% of the sample was Hispanic. Five participants (3.5%) previously used any CNS stimulants. ADHD was diagnosed using the Disruptive Behavior Disorders (DBD) Structured

Interview,²⁵ by masters-level or higher clinicians, combined with parent and teacher ratings.²⁶ Psychiatric comorbidity was assessed by the NIMH Diagnostic Interview Schedule for Children IV, computerized version,²⁷ with comorbid disorders allowed if ADHD was more impairing. Diagnoses were confirmed by two MD/PhD faculty.

Procedures

All procedures were approved by the Western Institutional Review Board and the study was registered at ClinicalTrials.gov (NCT01109849). Written consent was obtained from parents and assent from children ages seven plus. At baseline, participants were randomized to medication plus low intensity behavioral treatments (78%) or high intensity behavioral treatments without medication (22%) (Figure 1; available at www.jpeds.com). As planned, 180 were randomized to medication, with 165 taking at least one dose. All ADHD medications were prescribed through the study under open label conditions. This observational analysis included the 141 participants (61% of the original sample) using study medication for at least 50% of weekdays for any continuous 6-month period. There were 24 participants who did not use sufficient medication to qualify for inclusion into this analysis. Participants were initially treated with OROS-Methylphenidate (MPH), starting at 18 mg with dose titrated every two weeks until optimized using parent and teacher ratings.^{26, 28, 29} Optimal dose was defined as a tolerable dose producing good home and school functioning with no meaningful room for improvement. Doses could be increased up to the FDA age maximum or 2mg/kg per day of MPH,¹⁰ whichever was lower. This optimization phase could last up to 12 weeks with a dose having to be stable for two consecutive visits to be optimized. If OROS-MPH was not efficacious or tolerable, alternative MPH (immediate release MPH, dexamethylphenidate ER or other sprinkle ER MPH capsules) or amphetamine products (immediate or ER mixed amphetamine salts or lisdexamfetamine) were

7
prescribed. Study treatment lasted 30 months. After study month six, participants with persistent impairment could cross over to the other arm (e.g. medication or higher intensity behavior therapy). Of the 141 in this analysis, 21 (15%) were initially assigned to the behavior therapy arm and later crossed to medication. Once optimized, dose could be adjusted after 6 months of medication use if moderate or worse severity was scored on the Clinical Global Impressions Severity Scale (CGI-S),³⁰ as long as the participant was not assigned to WRT.

Height, weight, BMI, side effects and ADHD symptom ratings from parents were collected at every visit. For those starting medication at entry, assessments were completed at week 0, 2, 4, 6, 8, 10, 12, 16, 20, 24 and months 9, 12, 15, 18, 21, 24, 27, 30. The numbers of pills taken were recorded at each visit, and parents completed a monthly medication log. For those starting medication later, this assessment schedule began when medication was started (assessed every 3 months before that). After any six consecutive months on medication, participants with a $>.5$ z-unit decline in BMI were randomized to one of three WRTs.²⁴ All participants in WRT had their stimulant dose capped and stayed in WRT until their BMI percentile returned to baseline or were cleared by study nutritionist to end WRT. During WRT, ratings were completed monthly. In this analysis, 69 (49%) participants met WRT criteria. For those never entering WRT, at least 18 assessment visits were completed over the 30 months of the study.

Predictor Variables

Table 1 lists examined predictors and Table 2 (available at www.jpeds.com) presents descriptive statistics. The only significant difference between the entire study population and the subset in this observational analysis was for marital status of the primary caregiver.

Biometrics. These included gender and standardized height, weight and BMI when starting medication. Height and weight were collected with using standardized protocol and calibrated

stadiometer and scale.²⁴ Structural auxologic analysis was used to estimate the age of minimum growth velocity for each child that marks the transition from the childhood to the adolescent growth phases. The large variation in the timing of the transition between growth phases is not accounted by z-scores and could confound associations between medication exposure and growth velocity in models assuming a uniform age of onset across participants.³¹ A binary predictor was created to indicate whether the child started medication before or after the estimated age of minimum growth. Of the 141 participants, 19% (27) had entered the adolescent growth phase before baseline and 53 (37.5%) more entered it during the study. Mid-parental height was calculated using measurements from all available biological parents. For biological fathers, 67/119 (56%) of collected heights were measured and 52 (44%) were estimated from parental report.

DSM symptoms. Parents and teacher-rated symptoms of ADHD and oppositional defiant disorder (ODD) on the Disruptive Behavior Disorders Rating Scale prior to medication initiation were examined as predictor of weight, height and BMI trajectories.²⁶ Predictors included the mean item response of items measuring impulsivity/hyperactivity, inattention, or ODD symptoms.

Side Effects: Parents completed the Pittsburgh Side Effects Rating Scale (PSERS).³² It includes a specific item rating appetite suppression. PSERS was completed at every assessment, but only the first rating after dose optimization was examined as a predictor. Parent-rated “loss of appetite” was coded as being moderate or severe (versus none/mild) at this time point.

Medication. Predictors were created measuring the percent of days medicated and (the cumulative amount of MPH consumed. Medication data was derived from the daily medication logs and expressed in milligrams of MPH equivalents using the conversion formulas in the MTA.³³ Predictors were created separately for the first six months after starting medication and) the start of medication to end of follow-up (i.e., last available visit) to examine if different associations are

seen as medication use becomes more chronic. The median interval between the date of first medication and end of follow-up was 880 days (IQR = [758, 906]). Frequency was defined as percent of days medication was used over the assessment period. Time intervals for medication use were chosen to match the time intervals used for growth measurements, as described below.

Dependent Variables

Entered WRT. The first dependent variable was a binary indicator of whether the child ever entered WRT or not. To enter, participants must have lost > 0.5 z-units in BMI and been taking medication for at least 6 months. Participants who were above the 85th percentile for BMI at study entry had to lose > 1 z-unit of BMI and manifest raw weight loss to be assigned to WRT. Among the 141 participants, 69 (49%) participants entered WRT at any point during the study.

Change in z-BMI, z-weight, z-height across follow-up. We computed variables estimating the change observed in the first 6 months after starting medication and from the start of medication to end of follow-up (i.e., last available visit). Each timeframe has its own advantages. The impact of CNS stimulants on weight has been reported to be maximal over the first 6 months of use and between 24-30 months after medication initiation for height velocity.^{13, 16} The protocol ensured that children did not receive any weight recovery treatments for the first 6 months of medication use. The timeframe from the start of medication to the end of follow-up was included to maximize the amount of data for each child, recognizing the associations may be more difficult to interpret given imperfect adherence to medication over time. For each timeframe, all measurements after the date of first medication use to the end of the assessment period were used, regardless of medication status at follow-up assessments.

For the 6-month window, we used height and weight measurements taken closest to the target duration, accepting those taken with ± 1.5 months of this target. A change score was computed by subtracting the height/weight/BMI measurement taken at medication initiation from the corresponding measurement taken approximately 6 months later, dividing that quantity by the number of days elapsed between the two measurements and multiplying by 180 to rescale back to change over 6 months. Table 1 reports descriptive statistics for these change scores.

Change in z-weight as a predictor of change in z-height. To assess if initial weight changes are predictive of subsequent growth velocity, we included change in z-weight in the first 6 months of starting medication as a predictor of z-height change in the first 6 months after starting medication and from the start of medication to the end of follow-up (i.e., last available visit). We also included change in z-weight from medication start to the end of follow-up as a predictor of change in z-height over the entire follow-up period.

Analytic Plan

Missing data on predictors were rare except for midparental height (Table I). Data ranged from 87% to 100% complete for dependent variables. We estimated bivariate correlations between each predictor and each outcome in *Mplus* 8.³⁴ To account for missing data, the model was estimated using full-information maximum likelihood and the biometric predictors listed in Table 1 were included as auxiliary variables.^{35, 36} As a sensitivity analysis, we re-estimated associations of predictors with WRT entry, excluding those with BMI > 85th percentile at baseline, as they had a different criterion for entry to WRT ($n = 39$ of 141). We also repeated the analyses of baseline biometrics predicting change in weight, height and BMI month 0 to 6 using percentage change in raw values over this timeframe versus change in z scores as even standardized units can become skewed at extreme range.³⁷ Finally, we report results for the first 12-months after starting

medication to produce estimates of annualized change in growth rates as these may allow for comparison with assessment periods employed in past reports¹⁷ and be a more readily interpretable metric for practicing clinicians. Procedures were identical to that used for the 6-month window.

Results

The mean dose at dose optimization was 22mg (6.1) MPH equivalents with a range of 10mg to 36mg per day. At last visit, mean dose for those using medication was 26.2mg (8.5) with range of 10 to 59mg. Of the 141 in this analysis, there were 131 (93%) participants with at least 12 months of medication use and 101 (71.6%) with at least 24 months of use. There were 118 (83.7%) that completed the final 30 month assessment regardless of medication status at endpoint. No child discontinued medication over growth concerns, but one child had medication stopped due to weight loss after assignment to drug holiday and caloric supplementation was not sufficient.

Table 3 reports the correlations of each predictor with each dependent variable. Only statistically significant associations are described below. Figure 2 shows the probability of entering WRT as a function of MPH exposure. Figure 3 shows how the correlation of changes in z-BMI, z-weight, and z-height with percent of days medicated and total exposure to MPH evolve over time.

Correlates of Entry to Weight Recovery Treatment

Children with greater z-height ($r = -0.20$), z-weight ($r = -0.44$), or z-BMI ($r = -0.45$) at medication start were less likely to enter WRT (p 's $< .05$). Children medicated on more days in the first 6 months of use ($r = 0.37$) or over the entire follow-up period ($r = 0.32$) were more likely to enter WRT (p 's $< .001$). Children using more MPH during the first 6 months ($r = 0.33$; Figure 2) or during the length of follow-up ($r = 0.28$) were more likely to enter WRT (p 's $< .001$).

Correlates of Changes in z-BMI

First 6 months after starting medication. Children with greater z-height ($r = 0.19$), z-weight ($r = 0.28$), or z-BMI ($r = 0.20$) when starting medication exhibited less reduction in z-BMI. Children medicated on a greater percentage of days ($r = -0.36$) or using more total milligrams ($r = -0.36$) in the first 6 months on medication exhibited greater reduction in z-BMI (p 's $< .05$).

Start of medication to end of follow-up. Older children exhibited less reductions in z-BMI ($r = 0.20$, $p < .05$). Children who were medicated on a greater percentage of days ($r = -0.38$) or used more total milligrams ($r = -0.23$) exhibited greater reduction in z-BMI (p 's $< .05$).

Correlates of Changes in z-Weight

First 6 months after starting medication. Children with greater z-height ($r = 0.24$) or z-weight ($r = 0.28$) when starting medication exhibited less reduction in z-weight. Children whose parents rated them as experiencing moderate or severe loss of appetite during dose optimization exhibited greater reductions in z-weight ($r = -0.20$, $P < .05$). Children medicated on a greater percentage of days ($r = -0.38$) or using more milligrams ($r = -0.34$) in the first 6 months of medication use exhibited greater reduction in z-weight (p 's $< .05$).

Start of medication to end of follow-up. Children who were older ($r = 0.19$, $p < .05$) or started medication after the projected age of slowest growth exhibited less reductions in z-weight ($r = 0.18$, $p < .05$). Children whose parents rated them as experiencing moderate or severe appetite loss during dose optimization exhibited greater reductions in z-weight ($r = -0.19$, $p < .05$). Children medicated on a greater percentage of days ($r = -0.40$) or using more milligrams ($r = -0.30$) exhibited greater reduction in z-weight (p 's $< .001$).

Correlates of Changes in z-Height

First 6 months after starting medication. Older children ($r = 0.30, p < .05$) or those past the projected age of slowest growth exhibited less z-height reductions ($r = 0.28, p < .05$). Children experiencing moderate/severe appetite loss exhibited more decline in z-height ($r = -0.28, p < .01$).

Start of medication to end of follow-up. Females exhibited less reductions in z-height ($r = 0.17, p < .05$). Children who were medicated on a greater percentage of days ($r = -0.26$) or used more milligrams ($r = -0.32$) over the study exhibited greater z-height reductions (p 's $< .05$).

Change in z-weight as predictor. Children who exhibited less reductions in z-weight over the first 6 months of medication use exhibited less reductions in z-height over the entire follow-up period ($r = 0.20, p < .05$). Children who exhibited less reductions in z-weight over the full duration of follow-up exhibited less reductions in z-height over the same interval ($r = 0.42, p < .001$).

Sensitivity Analyses

Excluding those with entry BMIs ≥ 85 th percentile who had modified WRT criteria produced small changes in the magnitude of predictors' correlations (Table 4 and Figure 4; both available at www.jpeds.com). There were only two appreciable changes: the correlation of entry z-BMI with WRT entry ($r = -0.45, p < .05$ vs $r = -0.18, ns$) and BMI z-score prior to medication with BMI change over 6 months ($r = -0.2, p < .05$ vs $r = 0.11, ns$) were no longer significant.

When the percentage change in raw height/weight/BMI were used as outcomes versus standardized (z) scores, z-weight score when starting medication was significantly correlated with the 6-month change in height. Children of lower standardized weight at medication start experienced smaller height increases than heavier children at medication start ($r = 0.21, p < .05$). BMI at medication start predicted change in height over 6 months ($r = 0.18, p < .05$).

Over 12 months of medication use (Table 4), percent days medicated (r 's $= -0.24$ to -0.38 , p 's $< .001$) and total mg of medication (r 's $= -0.18$ to -0.35 , p 's $< .05$) predicted change in z-BMI, z-

weight and z-height. Age predicted all three change scores (r 's=0.22-0.25, $p<.05$). Starting medication after the age of minimal growth velocity predicted change in z-weight ($r=0.18$, $p<.05$) and z-height ($r=0.23$, $p<.05$). Children with less reductions in z-weight over the first 6 months of medication exhibited less z-height change over the first 12 months of use ($r=.28$, $p<.01$). Parent ratings of appetite at dose optimization predicted change in z-height ($r=-0.21$, $p<.05$).

Discussion

The aim of this analysis was to identify predictors of height, weight, and BMI change in medication naïve children with ADHD initiating CNS stimulants. Total MPH exposure was robustly correlated with changes in z-weight and BMI for each assessment period, for height over the study's duration and for entry to weight recovery treatments. Older participants and those starting medication after the projected onset of the adolescent growth phase experienced less weight suppression over the study's duration and less height suppression during the first 6 months on medication. Females experienced less height suppression than males. There was no evidence that children of short stature or low weight at medication initiation were at reduced risk for decelerations in weight or height velocity. Children with smaller standardized weights or heights at medication initiation experienced greater reductions in z-weight and BMI over the first 6 months of medication use. Parent ratings of appetite suppression proved to be useful indices of changes in weight and height velocity, but ADHD or ODD symptom severity did not predict changes in either.

Similar to prior work, there were robust associations with medication exposure and change in standardized weight and BMI.^{22, 38, 39} Associations emerged by month 6 and persisted for the study's duration. Findings were not driven by overweight youth declining to healthier weights. As weight deficits early in care may lead to stopping treatment,^{20, 21} stabilizing weight may improve treatment adherence, which is often poor.^{40, 41} Although weight deficits may persist in childhood

when medication is continued, a different trajectory emerges in adolescence. In the MTA, BMI declined when medication was started (mean entry age was 8.4). After year two, BMI increased in ADHD participants using medication, surpassing levels in non-ADHD controls.¹⁵ Other studies have reported similar patterns,⁴² and a meta-analysis reported strong links between childhood ADHD and higher BMI into adulthood.⁴³ Given the appreciable morbidity risks with obesity,^{44, 45} it seems prudent to limit efforts to increase weight in children prescribed CNS stimulants to those with medically concerning weight loss or with suppressed weight velocities into adolescence.

In the MTA³³ and here, frequency of medication use predicted growth velocity despite the large differences in medication exposure across the studies, likely due to the 16 year assessment period for the MTA versus 30 months for this study. Over 30-months in this study, youth assigned to WRT grew 1.4cm less than expected and 1.7cm less than ADHD youth not using medication.²⁴ No evidence was found that drug holidays on non-school days increased growth velocity over a two year period, suggesting that medication cessation may be necessary to see meaningful growth accelerations over this time period. In the MTA, initiating medication at an early age and continuing it through adolescence had the greatest impact on height, with no evidence of meaningful catch-up growth while medication was used. Consistent users were 4.1cm shorter than negligible users and 3.3cm shorter than non-ADHD controls.¹⁵ Neither study could assess the impact of dosing schedules on growth beyond these comparisons. Behavioral therapies delay the onset of ADHD medication use⁴⁶ and reduce the mean dose of medication needed.⁴⁷ Therefore, behavioral therapies may be an effective means to preserve growth by reducing medication exposure, especially during young ages when medication impacts on growth may be greater.⁴⁸

Most prior work assessing medication effects on weight and height has focused on dose measured as mg/kg/day and found mixed results.^{13, 17, 39, 49} In this protocol, all stimulant medication

was dispensed through the study, enabling more precise estimates of actual medication exposure. Correlations with height, weight and BMI change were comparable when frequency of use or total medication exposure was the predictor. These results suggest that how often medication is used may be at least as impactful as the daily dose.

With their extended therapeutic duration, ER CNS stimulants give parents more opportunity to observe medication effects on appetite.⁵⁰ Parent ratings after dose was optimized predicted weight change at month 6 with a trend for weight change at the last assessment. The association with height change was unexpected but is consistent with the theory that negative caloric balance contributes to the growth suppression with CNS stimulants.^{17, 39} This theory is further supported by significant correlations observed between changes in weight and height. Weight change over the study was the most robust predictor of height change. However, weight restoration did not lead to increased height velocity in this sample²⁴ or in the MTA.¹⁵ Likewise, in adolescents with anorexia nervosa, weight restoration does not translate to improved height velocity.⁵¹ It appears that although appetite and weight loss may be predictive of a slowing in growth velocity, increasing weight is an insufficient means to accelerate growth.

We employed a brief public domain measure completed by parents to measure appetite loss and other side effects of CNS stimulants.³² Structured side effect ratings during dose optimization may be an inexpensive means to identify children at risk for concerning weight loss and even growth suppression. Parent ratings of appetite loss during early medication initiation could be used to identify children who should be preferentially targeted for early integration of behavioral therapies or other strategies to preserve growth. These ratings may be particularly valuable when direct assessment is challenging, such as during the current pandemic.^{52, 53}

Prior reviews observed the greatest declines in height and weight velocity in the tallest and heaviest youth at medication initiation, suggesting that children of low weight or small stature may be at reduced risk.¹⁷ However, many studies enrolled chronically medicated youth. The greatest declines in growth velocity occur during the first 1-2 years of medication use,^{15, 54} with rates stabilizing but not recovering from year 3 onward. Mixing treatment naïve and treated children in one sample may blunt the degree of observed growth suppression and make it appear that shorter and lighter children are protected from growth suppression when they actually acquired it prior to entry.⁵⁵ Our study eliminated the confound of prior medication status which may be why we failed to find a protective effect of short stature or low weight. We found that lighter and shorter youth were at increased risk for reductions in z-weight and z-BMI and were more likely to need WRT interventions. To be consistent with past work,¹⁷ we also measured change in height, weight and BMI using raw units. Results for change in weight were comparable, but low entry weight and BMI now predicted smaller height gains, which was not seen when z-units were the outcome. It is reassuring that studies of children with ADHD and short stature have not found diminished effect of growth hormone on height velocity when CNS stimulants are also used.^{56, 57} However, the results observed here suggest that children of small stature or low weight should be cautiously prescribed CNS stimulants and have their weight and height velocity routinely monitored. Nonstimulant options or behavioral treatments offer a potentially more tolerable initial treatment options for children already struggling to reach a medically appropriate weight or height.⁵⁸⁻⁶⁰

As expected, older age and being in the adolescent growth phase when starting medication were associated with larger gains in weight and height. This was likely because these participants would have experienced a period of faster growth during the assessment period. When measured using standardized or raw height, females experienced less declines in standardized height. They

were more likely than males to be in the adolescent growth phase during the study, probably due to gender effects on the timing of the adolescent growth spurt.³¹ The majority of participants in this study and in other growth assessments of ADHD samples were male.¹³ Therefore, results should be applied with caution to females, especially in samples that are still growing, given the impact of gender on the timing of the adolescent growth spurt. For example, weight is more strongly correlated with pubertal onset in females than males,⁶¹ so correlations of weight and height changes may vary by gender. We examined whether symptom severity for ADHD/ODD would be predictive of change in weight or growth as it has been proposed that the two could be correlated.^{16, 49, 62} Symptom severity is an easily and frequently assessed metric in primary care, but we observed no consistent correlations with any symptom dimensions and auxologic outcomes.

After removal of participants with a BMI% >85th at study entry, all medication findings remained significant despite the reduced sample size. Several of the associations between biometric growth predictors and auxologic outcomes weakened. However, the weakening was minimal except for the correlations between premedication z-BMI with WRT entry and with change in BMI over the first 6 months of medication use. Elevated BMI is more likely as children age and correlates with earlier pubertal onset, which may explain why excluding children between the 85th and 95th BMI % preferentially impacted correlations with BMI change.⁶³

The primary limitation of this observational analysis is that participants were not protected by randomization as we included all participants regularly using medication over any 6-month period during the study regardless of their initial randomized assignments to medication or non-medication arms. Therefore, causal relationships between predictors and outcomes should not be assumed as it is possible the observed associations with medication and biometric outcomes could be due to other factors. Although 30 months is an extended duration for an ADHD treatment

study and longer than many prospective ADHD trials assessing growth,^{13, 14, 17} it did not track participants long enough to assess the impact of the adolescent growth spurt and to see if height deficits persisted into adulthood. The MTA did track into adulthood, observing that acquired deficits persist as long as medication is consistently used.¹⁵ this study examined the impact of efforts to promote weight recovery on the change in growth and weight velocity in children prescribed CNS stimulants. Results may differ from routine clinical care where dose reductions may be more likely to occur before weight recovery efforts. Lastly, this study was run at a single research site, which may limit its generalizability.

In treatment naïve youth with ADHD change in weight was a significant predictor of both current and future growth velocity, and parent ratings of appetite suppression predicted weight change and initial height velocity. Adjusting the frequency of medication use or its dose may reduce the degree of acquired suppression in weight and height. In youth where height or weight are a preexisting concern, the efficacy and tolerability of CNS stimulant medication should be closely monitored after medication initiation to ensure a favorable risk to benefit ratio for continuing versus switching to alternative treatments.

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Figure Legends

Figure 1

Study Flowchart

Note. BMI = body mass index, ADHD = Attention-Deficit/Hyperactivity Disorder, CNS = Central Nervous System, MPH = methylphenidate, kg = kilograms. Reprinted from “A Randomized Controlled Trial of Interventions for Growth Suppression in Children With Attention-Deficit/Hyperactivity Disorder Treated With Central Nervous System Stimulants,” by J.G. Waxmonsky, 2020, *Journal of the American Academy of Child & Adolescent Psychiatry*, 59, p. 1333. Copyright 2020 by the Elsevier. Reprinted with permission.

Figure 2

Association Between Cumulative MPH Intake in First Six Months and Probability of Qualifying for Weight Recovery Treatment

Note. MPH=methylphenidate. Line is model-estimated probability of entering weight recovery treatment (WRT) (from univariate logistic regression). Grey ribbon indicates 95% confidence interval. Dots are the observed proportion of children (i.e., empirical probability) in each quartile of cumulative dose that met WRT criteria (position along x-axis indicates mean dose within quintile). Data are from children ever taking medication ($n = 141$).

Figure 3

Association Between Medication History Parameters and Changes in z-BMI, z-Weight, and z-Height Across Follow-Up

Note. BMI = body mass index, MPH = methylphenidate. Shows how the correlations between the medication use and change in body measurements evolve across time. Medication usage is calculated over the same interval as change in body measurements (e.g., leftmost red square in the left panel indicates correlation of change in z-BMI in the first 6 months of medication with the percent days medicated in first 6 months after starting medication). Percent days medicated and cumulative intake exhibit large correlations with changes in z-BMI and z-weight that are present

at 6 months and persist through the end of follow-up. In contrast, the correlation of percent days medicated and cumulative intake with changes in z-height remains small at 6 months before growing over the follow up period.

Figure 4

Sensitivity Analysis 1: Excluding Children Above the 85th Percentile in BMI at Study Entry

Note. AUXAL = structural auxologic analysis model, BMI = body mass index, ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, MPH = methylphenidate, kg = kilograms. Compares correlations based on all children who took medication (black circles) with correlations based on only those with entry BMI below the 85th percentile (white circles). Pairs of correlations with a box around them differed in statistical significance (i.e., one above and one below a threshold of $p < .05$). As shown, excluding those with entry BMI above the 85th percentile generally had little impact on the magnitude or statistical significance of observed correlations.

Table 1
Descriptive Statistics for Variables

Category	Variable	Proportion	Mean	SD	Range [Min, Max]	Percentage Missing
Independent variable	Female	27 %	-	-	-	0%
	Age in years at start of medication		8.3	1.9	[5.1, 15]	1%
	Started medication after AUXAL-projected age of slowest growth	19 %	-	-	-	1%
	Height (z) at start of medication		0.04	0.96	[-2.43, 3.04]	2%
	Weight (z) at start of medication		0.34	0.89	[-2.42, 2.60]	1%
	BMI (z) at start of medication		0.46	0.85	[-1.63, 2.24]	2%
	Midparental height in centimeters (measured or reported)		172.9	7.6	[153.1, 190.0]	16%
	Parent rating of hyperactivity/impulsivity symptoms of ADHD at study entry		1.79	0.74	[0, 3]	6%
	Parent rating of inattention symptoms of ADHD at study entry		2.13	0.65	[0.33, 3]	6%
	Parent rating of ODD symptoms at study entry		0.98	0.69	[0, 2.88]	6%
	Parent rating of loss of appetite at optimization was moderate/severe	26 %	-	-	-	6%
	Percent of days medicated in first 6 months after starting medication		0.72	0.17	[0.37, 1]	0%
	Percent of days medicated in first 12 months after starting medication		0.68	0.17	[0.28, 1]	0%
	Percent of days medicated from start of medication to last available visit		0.63	0.19	[0.14, 1]	7%
	Total MPH intake (kg) in first 6 months after starting medication		2.82	1.08	[0.18, 6.01]	0%
	Total MPH intake (kg) in first 12 months after starting medication		5.54	2.41	[0.48, 15.52]	0%
	Total MPH intake (kg) from start of medication to last available visit		12.1	7.53	[0, 44.68]	0%
Dependent variable	Met criteria for Weight Recovery Treatment (WRT)	49 %	-	-	-	0 %
	Change in BMI (z) from start of medication to +6 months		-0.42	0.35	[-1.70, 0.17]	9 %
	Change in BMI (z) from start of medication to +12 months		-0.36	0.31	[-1.32, 0.28]	13 %
	Change in BMI (z) from start of medication to last available visit		-0.31	0.49	[-1.78, 1.05]	10 %
	Change in weight (z) from start of medication to +6 months		-0.30	0.23	[-0.96, 0.19]	7 %
	Change in weight (z) from start of medication to +12 months		-0.31	0.24	[-0.92, 0.27]	13 %
	Change in weight (z) from start of medication to last available visit		-0.30	0.44	[-1.58, 0.86]	9 %
	Change in height (z) from start of medication to +6 months		-0.05	0.12	[-0.34, 0.33]	9 %
	Change in height (z) from start of medication to +12 months		-0.11	0.18	[-0.66, 0.44]	13 %
	Change in height (z) from start of medication to last available visit		-0.16	0.39	[-1.13, 1.10]	10 %

Note. SD = standard deviation, Min = minimum, Max = maximum, AUXAL = structural auxologic analysis model, BMI = body mass index, ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, MPH = methylphenidate, kg = kilograms. Based on available data from $N = 141$ participants.

Table 2
Characteristics at Study Entry of those Included versus. Excluded from Analyses

Variable	Included in this sample (n = 141)	Excluded from this subsample (n = 88)
Child is female	27 %	26 %
Child age in years	8.0 (1.9)	8.1 (2.0)
Child is Hispanic	72 %	74 %
Child is Black	10 %	13 %
Primary caregiver is married*	66 %	52 %
Primary caregiver has BA	53 %	53 %
Number of ODD symptoms	2.3 (2.2)	2.2 (2.2)
Number of CD symptoms	0.5 (0.9)	0.4 (1.0)
Standardized height	0.04 (0.98)	0.12 (1.02)
Standardized weight	0.31 (0.91)	0.31 (0.88)
Standardized BMI	0.43 (0.86)	0.39 (0.82)

Participants in the larger study were excluded from this analysis if they did not use medication for at least 6 months. *Note.* BA = Bachelor's degree, ODD = Oppositional Defiant Disorder, CD = Conduct Disorder, BMI = body mass index. Number of ODD/CD symptoms is per parent report. * = $p < .05$

Table 3

Correlates of Entering Weight Recovery Treatment and Changes in z-BMI, z-Weight, and z-Height After Starting Methylphenidate

Predictor	Entered Weight Recovery Treatment (WRT)		Δ z-BMI from 0 to 6 months		Δ z-BMI from 0 months to end of follow-up		Δ z-weight from 0 to 6 months		Δ z-weight from 0 months to end of follow-up		Δ z-height from 0 to 6 months		Δ z-height from 0 months to end of follow-up	
	Correlation (SE)	Sig.	Correlation (SE)	Sig.	Correlation (SE)	Sig.	Correlation (SE)	Sig.	Correlation (SE)	Sig.	Correlation (SE)	Sig.	Correlation (SE)	Sig.
Biometrics														
Female	+0.04 (0.08)		-0.02 (0.09)		-0.03 (0.09)		-0.04 (0.09)		-0.01 (0.09)		+0.16 (0.08)		+0.17 (0.09)	*
Age in years at start of medication	-0.13 (0.08)		+0.09 (0.09)		+0.20 (0.09)	*	+0.12 (0.09)		+0.19 (0.09)	*	+0.30 (0.08)	***	+0.16 (0.09)	
Started medication after AUXAL-projected age of slowest growth	-0.09 (0.08)		+0.04 (0.09)		+0.12 (0.09)		+0.08 (0.09)		+0.18 (0.08)	*	+0.28 (0.08)	**	+0.14 (0.09)	
Height (z) at start of medication	-0.20 (0.08)	*	+0.19 (0.08)	*	+0.14 (0.09)		+0.24 (0.08)	**	+0.10 (0.09)		-0.07 (0.09)		-0.13 (0.09)	
Weight (z) at start of medication	-0.44 (0.07)	***	+0.28 (0.08)	**	+0.07 (0.09)		+0.28 (0.08)	***	+0.05 (0.09)		+0.08 (0.09)		+0.00 (0.09)	
BMI (z) at start of medication	-0.45 (0.07)	***	+0.20 (0.08)	*	-0.01 (0.09)		+0.16 (0.08)		-0.01 (0.09)		+0.15 (0.09)		+0.05 (0.09)	
Midparental height in centimeters (measured or reported)	-0.09 (0.09)		+0.06 (0.09)		+0.10 (0.09)		+0.11 (0.09)		+0.11 (0.09)		-0.10 (0.09)		-0.07 (0.09)	
Biometric deltas														
Change in weight (z) from start of medication to +6 months	-		-		-		-		-		+0.14 (0.09)		+0.20 (0.09)	*
Change in weight (z) from start of medication to last available visit	-		-		-		-		-		-		+0.42 (0.07)	***
Symptoms														
Parent rating of hyperactivity/impulsivity symptoms of ADHD at study entry	-0.08 (0.09)		-0.05 (0.09)		-0.06 (0.09)		-0.04 (0.09)		-0.05 (0.09)		-0.01 (0.09)		-0.08 (0.09)	
Parent rating of inattention symptoms of ADHD at study entry	+0.06 (0.09)		+0.06 (0.09)		-0.09 (0.09)		+0.08 (0.09)		-0.07 (0.09)		+0.02 (0.09)		+0.02 (0.09)	
Parent rating of ODD symptoms at study entry	-0.15 (0.08)		+0.03 (0.09)		-0.09 (0.09)		+0.03 (0.09)		-0.12 (0.09)		-0.07 (0.09)		-0.12 (0.09)	
Medication														
Parent rating of loss of appetite at optimization was moderate/severe	+0.10 (0.09)		-0.14 (0.09)		-0.14 (0.09)		-0.20 (0.09)	*	-0.19 (0.09)	*	-0.28 (0.08)	**	-0.16 (0.09)	
Percent of days medicated in first 6 months after starting medication	+0.37 (0.07)	***	-0.36 (0.07)	***	-		-0.38 (0.07)	***	-		-0.12 (0.09)		-	
Percent of days medicated from start of medication to last available visit	+0.32 (0.08)	***	-		-0.38 (0.08)	***	-		-0.40 (0.07)	***	-		-0.26 (0.08)	**
Total MPH intake (kg) in first 6 months after starting medication	+0.33 (0.07)	***	-0.36 (0.08)	***	-		-0.34 (0.08)	***	-		+0.05 (0.09)		-	
Total MPH intake (kg) from start of medication to last available visit	+0.28 (0.08)	***	-		-0.23 (0.09)	*	-		-0.30 (0.09)	***	-		-0.32 (0.08)	***

Note. SE = standard error, AUXAL = structural auxologic analysis model, BMI = body mass index, ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, MPH = methylphenidate, kg = kilograms.

Correlations are Pearson correlations. "Sig." indicates statistical significance of correlation. All models were estimated using full-information maximum likelihood and included the 141 children who ever took medication. Auxiliary variables were female, age in years at study entry, entered study after AUXAL-projected age of slowest growth, z-height at study entry, z-weight at study entry, and z-BMI at study entry.

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 4

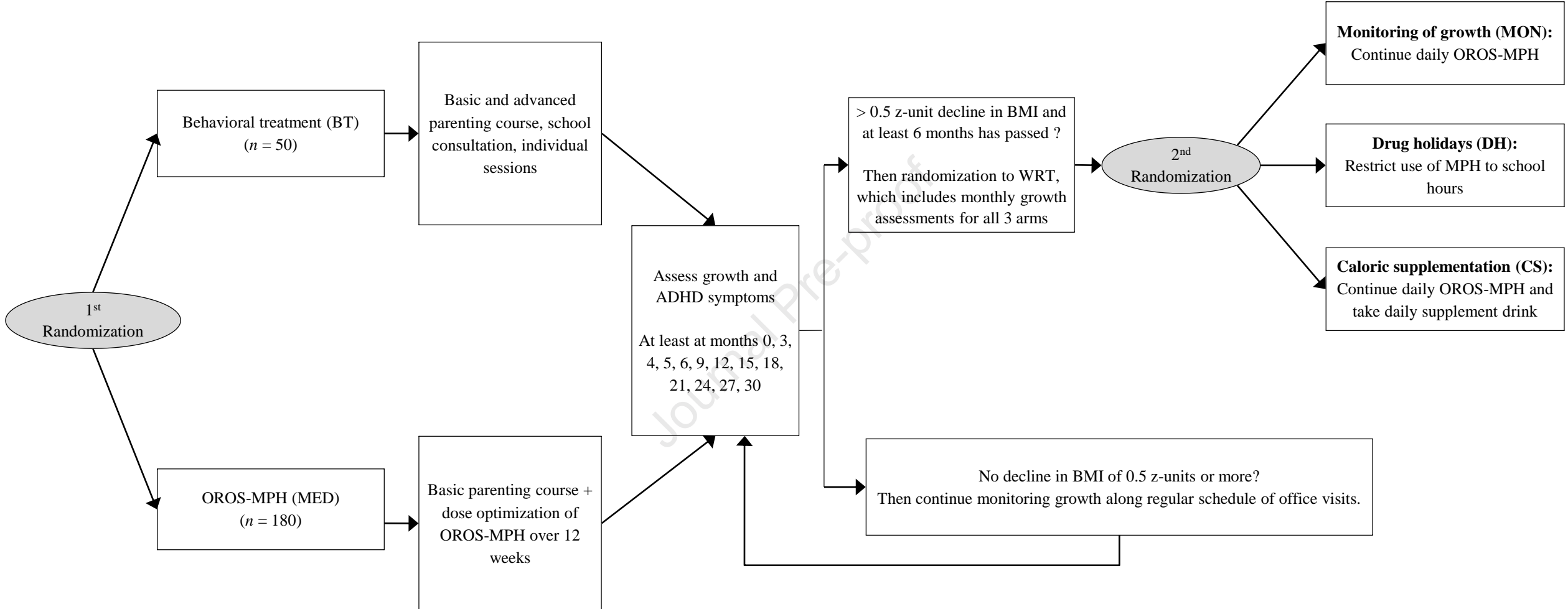
Correlates of Entering Weight Recovery Treatment and Changes in z-BMI, z-Weight, and z-Height in the First 12 Months After Starting Methylphenidate

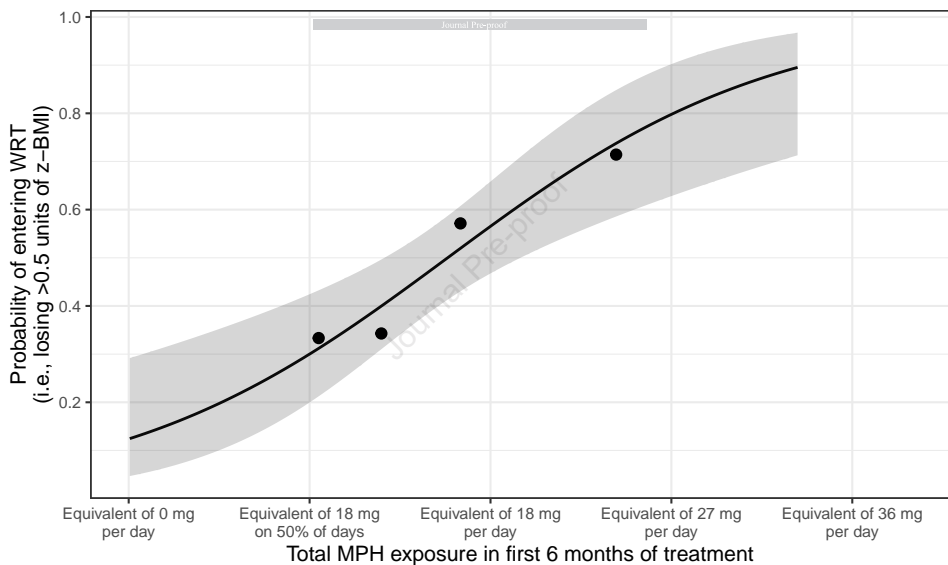
Predictor	Δ z-BMI from 0 to 12 months Correlation (SE)	Sig.	Δ z-weight from 0 to 12 months Correlation (SE)	Sig.	Δ z-height from 0 to 12 months Correlation (SE)	Sig.
Biometrics						
Female	-0.06 (0.09)		-0.09 (0.09)		+0.12 (0.09)	
Age in years at start of medication	+0.22 (0.09)	*	+0.23 (0.09)	*	+0.25 (0.09)	**
Started medication after AUXAL-projected age of slowest growth	+0.13 (0.09)		+0.18 (0.09)	*	+0.23 (0.08)	**
Height (z) at start of medication	+0.06 (0.09)		+0.12 (0.09)		-0.06 (0.09)	
Weight (z) at start of medication	+0.01 (0.09)		+0.04 (0.09)		+0.08 (0.09)	
BMI (z) at start of medication	-0.04 (0.09)		-0.05 (0.09)		+0.12 (0.09)	
Midparental height in centimeters (measured or reported)	+0.06 (0.09)		+0.12 (0.09)		-0.04 (0.09)	
Biometric deltas						
Change in weight (z) from start of medication to +6 months	-		-		+0.28 (0.08)	**
Change in weight (z) from start of medication to +12 months	-		-		+0.38 (0.08)	***
Symptoms						
Parent rating of hyperactivity/impulsivity symptoms of ADHD at study entry	-0.14 (0.09)		-0.15 (0.09)		-0.07 (0.09)	
Parent rating of inattention symptoms of ADHD at study entry	+0.05 (0.09)		+0.04 (0.09)		-0.01 (0.09)	
Parent rating of ODD symptoms at study entry	+0.07 (0.09)		+0.03 (0.09)		-0.10 (0.09)	
Medication						
Parent rating of loss of appetite at optimization was moderate/severe	-0.02 (0.09)		-0.10 (0.09)		-0.21 (0.09)	*
Percent of days medicated in first 12 months after starting medication	-0.37 (0.08)	***	-0.37 (0.08)	***	-0.24 (0.09)	**
Total MPH intake (kg) in first 12 months after starting medication	-0.35 (0.08)	***	-0.35 (0.08)	***	-0.18 (0.09)	*

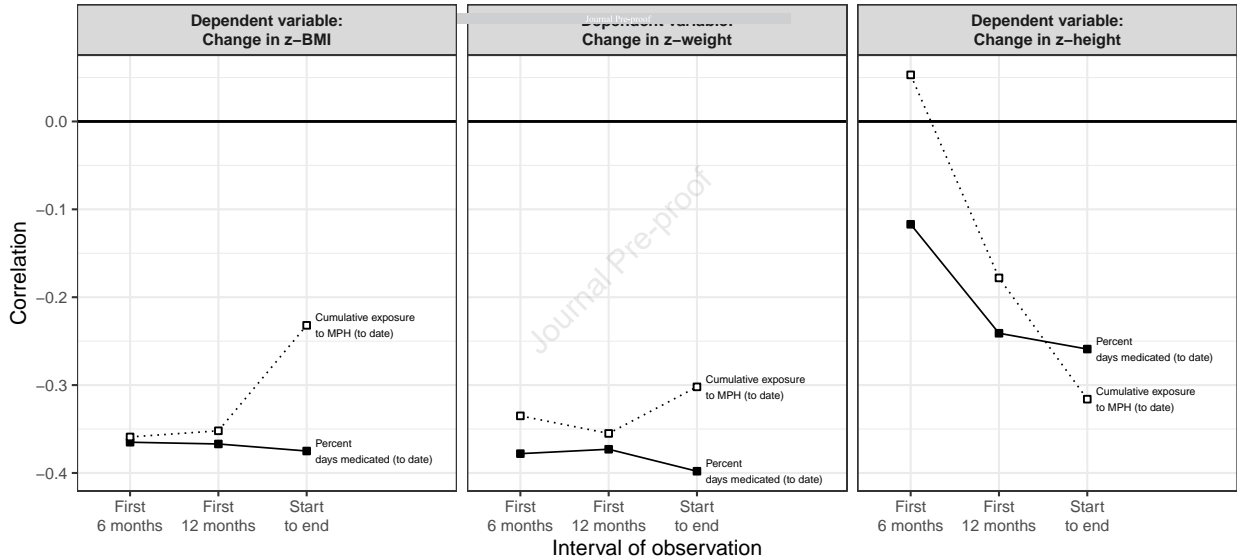
Note. SE = standard error, AUXAL = structural auxologic analysis model, BMI = body mass index, ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, MPH = methylphenidate, kg = kilograms.

Correlations are Pearson correlations. "Sig." indicates statistical significance of correlation. All models were estimated using full-information maximum likelihood and included the 141 children who ever took medication. Auxiliary variables were female, age in years at study entry, entered study after AUXAL-projected age of slowest growth, z-height at study entry, z-weight at study entry, and z-BMI at study entry.

* $p < .05$, ** $p < .01$, *** $p < .001$







Group:

- All medicated children (N = 141)
- Medicated children with entry BMI below the 85th percentile (N = 102)

