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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Objective To identify predictors of changes in height, weight, and body mass index (BMI) in children with attention deficit hyperactivity disorder (ADHD) starting central nervous system (CNS) stimulants.

Study design There were 230 medication-naïve children aged 5-12 years with ADHD who 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 65 or more days in the first 6-months after starting medication. Biometric variables, ADHD, and oppositional defiant disorder symptom scores at medication initiation, and medication use over the study were examined as predictors of changes in standardized (z) 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 decreases over the first 6 months on medication. Greater appetite suppression during dose optimization predicted greater decreases in z-weight over the entire study and a greater decrease in z-height over the first 6 months on medication. z-weight change correlated with z-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 decreases in z-weight and z-BMI. Parent ratings of appetite during dose titration may serve as feasible indicators of future weight and height change in children using CNS stimulants. *(J Pediatr 2022;241:115-25)*.

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.[5-8] Anorexia and weight loss are often seen with CNS stimulants and can lead to treatment discontinuation.[1,9-12] CNS stimulants are associated with a standard mean difference of 0.27 for height and 0.33 for weight. The greatest 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 before enrollment who consistently used medication over the next decade. The greatest slowing in height velocity occurred in the first 2 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 in the 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, suggesting that initial weight loss could predict growth. Results about the impact of dose and age are mixed.[13,14,17-19] 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

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
CNS	Central nervous system
ER	Extended release
MTA	Multimodal Treatment of ADHD
ODD	Oppositional defiant disorder
WRT	Weight recovery treatment

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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 SDs for z-height, suggesting that shorter youth may develop meaningful suppression with CNS stimulants.[22]

Few treatment studies of attention deficit hyperactivity disorder (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 the 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 for 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 the predictors of standardized BMI, height, and weight changes for all participants recurrently using CNS stimulant medication in that study. The greatest decreases 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, and 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 aged 5-12 years meeting the criteria for any *Diagnostic and Statistical Manual of Mental Disorders IV* ADHD subtype. Exclusion criteria were an IQ of less than 70, BMI below the 5th percentile or above the 94th, use of CNS stimulants for more than 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 Structured Interview by masters-level or higher clinicians, combined with parent and teacher ratings.[25,26] Psychiatric comorbidity was assessed by the National Institute of Mental Health Diagnostic Interview Schedule for Children IV, computerized version, with comorbid disorders allowed if ADHD was more impairing.[27] Diagnoses were confirmed by 2 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 7 years and older. 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 participants were randomized to medication, with 164 taking at least 1 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 65 or more days within the first 6 months after starting medication, whch equates to using medicaion on at least 50% of weekdays over this period. There were 23 participants who did not use sufficient medication to qualify for inclusion in this analysis. Participants were initially treated with OROS-methylphenidate, starting at 18 mg with dose titrated every 2 weeks until optimized using parent and teacher ratings.[26,28,29] The 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 US Food and Drug Administration age maximum or 2 mg/kg/day of methylphenidate, whichever was lower.[10] This optimization phase could last up to 12 weeks, with a dose having to be stable for 2 consecutive visits to be optimized. If OROS-methylphenidate was not efficacious or tolerable, alternative methylphenidate (immediate release methylphenidate, dexmethylphenidate ER, or other sprinkle ER methylphenidate capsules) or amphetamine products (immediate or ER mixed amphetamine salts or lisdexamfetamine) were prescribed. Study treatment lasted 30 months. After study month 6, participants with persistent impairment could cross over to the other arm (eg, 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, as long as the participant was not assigned to WRT.[30]

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 weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, and 24 and months 9, 12, 15, 18, 21, 24, 27, and 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 6 consecutive months on medication, participants with a larger than 0.5 z-unit decrease in BMI were randomized to 1 of 3 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 participants (49%) 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 I lists examined predictors and **Table II** (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 sex and standardized height, weight, and BMI when starting medication. Height and weight were collected with using a 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. Midparental height was calculated using measurements from all available biological parents. For biological fathers, 67 of 119 (56%) of the collected heights were measured and 52 (44%) were estimated from parental report.

***Diagnostic and Statistical Manual of Mental Disorders* Symptoms.** Parent- and teacher-rated symptoms of ADHD and oppositional defiant disorder (ODD) on the Disruptive Behavior Disorders Rating Scale before medication initiation were examined as predictors 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.[32] It includes a specific item rating appetite suppression. The Pittsburgh Side Effects Rating Scale 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 (vs none/mild) at this time point.

Medication. Predictors were created measuring the percent of days medicated and the cumulative amount of methylphenidate consumed. Medication data were derived from the daily medication logs and expressed in milligrams of methylphenidate equivalents using the conversion formulas in the MTA.[33] Predictors were created separately for the first 6 months after starting medication and the start of medication to end of follow-up (ie, 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 to the date of last medication use was 886 days (IQR, 705-904). 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

Table I. Descriptive statistics for variables

Variables	Proportion (%)	Mean	SD	Range [Min to Max]	Percentage missing
Independent variables					
Female	27	–	–	–	0
Age in years at start of medication		8.3	1.9	[5.1 to 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 to 3.04]	2
Weight (z) at start of medication		0.34	0.89	[−2.42 to 2.60]	1
BMI (z) at start of medication		0.46	0.85	[−1.63 to 2.24]	2
Midparental height in centimeters (measured or reported)		172.9	7.6	[153.1 to 190.0]	16
Parent rating of hyperactivity/impulsivity symptoms of ADHD at study entry		1.79	0.74	[0 to 3]	6
Parent rating of inattention symptoms of ADHD at study entry		2.13	0.65	[0.33 to 3]	6
Parent rating of ODD symptoms at study entry		0.98	0.69	[0 to 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 to 1.00]	0
Percent of days medicated in first 12 months after starting medication		0.68	0.17	[0.28 to 1.00]	0
Percent of days medicated from start of medication to last available visit		0.63	0.19	[0.14 to 1.00]	7
Total methylphenidate intake (kg) in first 6 months after starting medication		2.82	1.08	[0.18 to 6.01]	0
Total methylphenidate intake (kg) in first 12 months after starting medication		5.54	2.41	[0.48 to 15.52]	0
Total methylphenidate intake (kg) from start of medication to last available visit		12.1	7.53	[0 to 44.68]	0
Dependent variables					
Met criteria for WRT	49	–	–	–	0
Change in BMI (z) from start of medication to +6 months		−0.42	0.35	[−1.70 to 0.17]	9
Change in BMI (z) from start of medication to +12 months		−0.36	0.31	[−1.32 to 0.28]	13
Change in BMI (z) from start of medication to last available visit		−0.31	0.49	[−1.78 to 1.05]	10
Change in weight (z) from start of medication to +6 months		−0.30	0.23	[−0.96 to 0.19]	7
Change in weight (z) from start of medication to +12 months		−0.31	0.24	[−0.92 to 0.27]	13
Change in weight (z) from start of medication to last available visit		−0.30	0.44	[−1.58 to 0.86]	9
Change in height (z) from start of medication to +6 months		−0.05	0.12	[−0.34 to 0.33]	9
Change in height (z) from start of medication to +12 months		−0.11	0.18	[−0.66 to 0.44]	13
Change in height (z) from start of medication to last available visit		−0.16	0.39	[−1.13 to 1.10]	10

AUXAL, structural auxologic analysis model.
Based on available data from 141 participants.
Parent ratings of ADHD/ODD symptoms at study entry could range from 0 to 3.

intervals used for growth measurements, as described elsewhere in this article.

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 more than 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 more than 1 z-unit of BMI and manifest raw weight loss to be assigned to WRT. Among the 141 participants, 69 (49%) 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 (ie, 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 and 30 months after medication initiation for height velocity.[13,16] The protocol ensured that children did not receive any WRTs 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 that 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 within ±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 2 measurements and multiplying by 180 to rescale back to change over 6 months. Table I 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 (ie, 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 (Muthén & Muthén).[34] To account for missing data, the model was estimated using full-information maximum likelihood and the biometric predictors listed in Table I were included as auxiliary variables.[35,36] As a sensitivity analysis, we re-estimated associations of predictors with WRT entry, excluding those with a BMI in the 85th percentile or greater at baseline, because they had a different criterion for entry to WRT (n = 39 of 141). We also repeated the analyses of baseline biometrics predicting changes in weight, height, and BMI from months 0 to 6 using percentage change in raw values over this timeframe vs change in z-scores, because 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 because these rates may allow for comparison with assessment periods used in past reports and be a more readily interpretable metric for practicing clinicians.[17] Procedures were identical to that used for the 6-month window.

Results

The mean dose at dose optimization was 22 mg (6.1) methylphenidate equivalents with a range of 10 mg to 36 mg/day. At the last visit, the mean dose for those using medication was 26.2 mg (8.5) with range of 10 to 59 mg. Of the 141 participants in this analysis, 131 (93%) were followed for at least 12 months after medication initiation and 101 (71.6%) for at least 24 months. There were 118 participants (83.7%) who completed the final 30-month assessment regardless of medication status at the end of the trial. No child discontinued medication over growth concerns, but 1 child had medication stopped due to continuing weight loss after assignment to drug holiday and caloric supplementation was not sufficient.

Table III reports the correlations of each predictor with each dependent variable. Only statistically significant associations are described in this report. Figure 2 shows the probability of entering WRT as a function of methylphenidate 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 methylphenidate evolve over time.

Correlates of Entry to WRT

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 (all $P < .05$). 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 (all $P < .001$). Children using more methylphenidate 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 (all $P < .001$).

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 of a decrease in the z-BMI. Children medicated on a greater percentage of days ($r = -0.36$) or using more total milligrams

Table III. Correlates of entering WRT and changes in z-BMI, z-weight, and z-height after starting methylphenidate

	Entered 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	
Predictors	**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 at start of medication, years	−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, cm (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 methylphenidate 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 methylphenidate 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)	‡

SE, standard error.

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.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

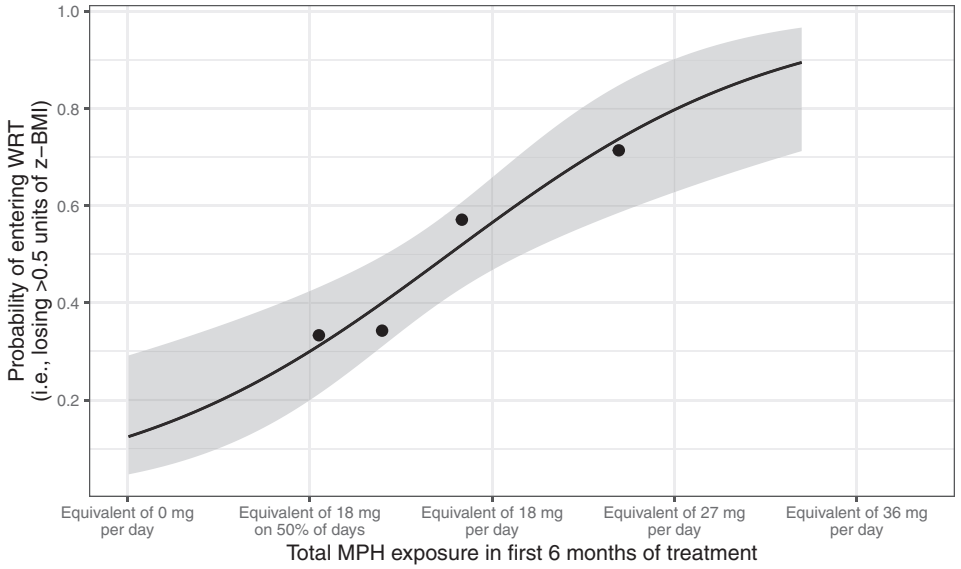

Figure 2. Association between cumulative methylphenidate intake in first 6 months and probability of qualifying for WRT. Line is model-estimated probability of entering WRT (from univariate logistic regression). Grey ribbon indicates 95% CI. Dots are the observed proportion of children (ie, empirical 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).

($r = -0.36$) in the first 6 months on medication exhibited greater decreases in z-BMI (all $P < .05$).

Start of Medication to End of Follow-up. Older children exhibited less decreases 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 decreases in z-BMI (all $P < .05$).

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

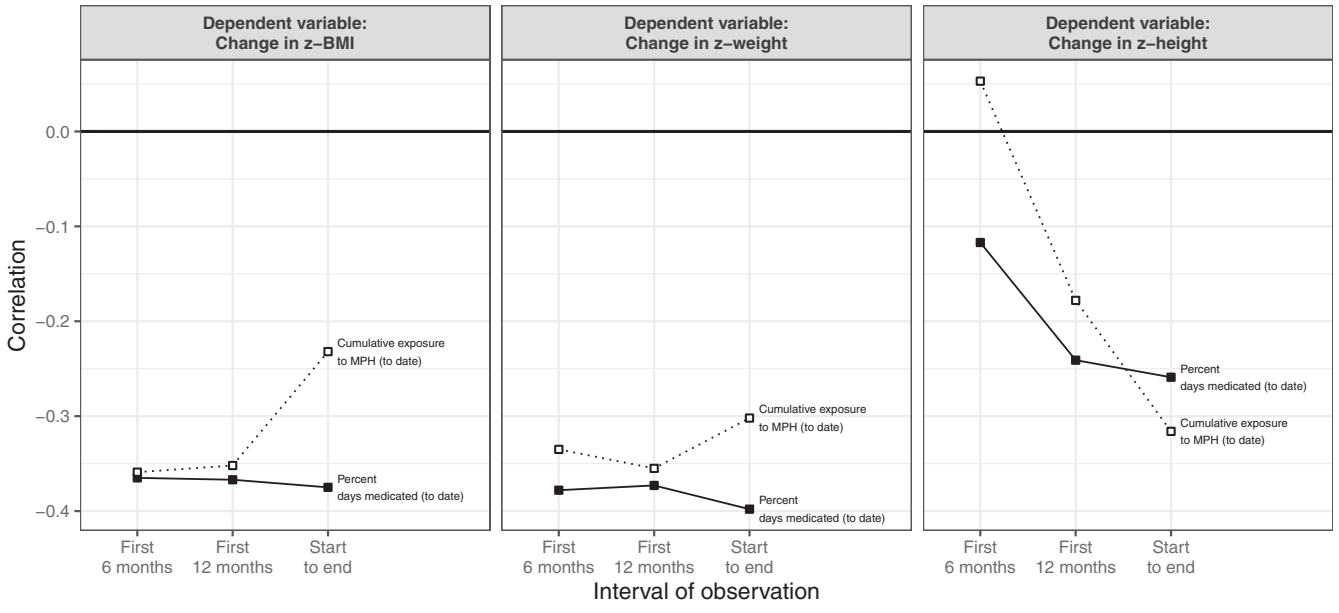

Figure 3. Association between medication history parameters and changes in z-BMI, z-weight, and z-height across follow-up. Shows how the correlations between the medication use and change in body measurements evolve across time. Medication use is calculated over the same interval as change in body measurements (eg, leftmost black 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.

starting medication exhibited less of a decrease in the z-weight. Children whose parents rated them as experiencing moderate or severe loss of appetite during dose optimization exhibited greater decreases 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 decreases in z-weight (all $P < .05$).

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 decreases 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 decreases 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 decreases in z-weight (all $P < .001$).

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 decreases ($r = 0.28$; $P < .05$). Children experiencing moderate/severe appetite loss exhibited a greater decrease in the z-height ($r = -0.28$; $P < .01$).

Start of Medication to End of Follow-up. Females exhibited less decreases 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 decreases (all $P < .05$).

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

Sensitivity Analyses

Excluding those with entry BMIs in the 85th percentile or greater who had modified WRT criteria produced small changes in the magnitude of predictors' correlations (**Figure 4**; available at www.jpeds.com). There was only 1 appreciable change: the correlation of z-BMI at the start of medication with WRT entry ($r = -0.45$; $P < .05$ vs $r = -0.18$, *ns*) at the start of medication was no longer significant.

When the percentage change in raw height/weight/BMI were used as outcomes vs 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 IV**; available at www.jpeds.com), the percent days medicated (all $r = -0.24$ to -0.37; all $P < .001$) and total milligrams of medication (all $r = -0.18$ to -0.35; all $P < .05$) predicted changes in z-BMI, z-weight, and z-height. Age predicted all 3 change scores (all $r = 0.22$-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 of a decrease in z-weight over the first 6 months of medication exhibited less z-height change over the first 12 months of use ($r = 0.28$; $P < .01$). 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. The total methylphenidate exposure was correlated robustly with changes in z-weight and BMI for each assessment period, for height over the study's duration, and for entry to WRTs. 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 a lesser risk for decelerations in weight or height velocity. Children with lower standardized weights or heights at medication initiation experienced greater decreases 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 decreasing to healthier weights. Because weight deficits early in care may lead to stopping treatment, stabilizing weight may improve treatment adherence, which is often poor.[20,21,40,41] Although weight deficits may persist in childhood when medication is continued, a different trajectory emerges in adolescence. In the MTA, BMI decreased when medication was started (mean entry age was 8.4 years). After year 2, the BMI increased in participants with ADHD using medication, surpassing levels in non-ADHD controls.[15] Other studies have reported similar patterns, with a meta-analysis reported strong links between childhood ADHD and higher BMI into adulthood.[42,43] Given the appreciable morbidity risks with obesity, 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.[44,45]

In the MTA and here, the frequency of medication use predicted growth velocity despite the large differences in

medication exposure across the studies, likely owing to the 16-year assessment period for the MTA vs 30 months for this study.[33] Over 30 months in this study, youth assigned to WRT grew 1.4 cm less than expected and 1.7 cm less than youth with ADHD not using medication.[24] No evidence was found that drug holidays on nonschool days increased growth velocity over a 2-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 4.1 cm shorter than negligible users and 3.3 cm 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 use and decrease the mean dose of medication needed.[46,47] Therefore, behavioral therapies may be an effective means to preserve growth by decreasing 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 milligrams per kilograms per 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 the 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 sample or in the MTA.[15,24] Likewise, in adolescents with anorexia nervosa, weight restoration does not translate to improved height velocity.[51] It seems 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 used 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 targeted preferentially 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 decreases 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 less of a 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, with rates stabilizing but not recovering from year 3 onward.[15,54] Mixing treatment-naïve and treated children in one sample may blunt the degree of observed growth suppression and make it seem that shorter and lighter children are protected from growth suppression when they actually acquired it before 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 decreases in z-weight and z-BMI and were more likely to need WRT interventions. To be consistent with past work, we also measured change in height, weight, and BMI using raw units.[17] The 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 prescribed CNS stimulants cautiously and have their weight and height velocity monitored routinely. 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 greater gains in weight and height. This finding 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 of a decrease in standardized height. They were more likely than males to be in the adolescent growth phase during the study, probably owing to sex 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, the results should be applied with caution to females, especially in samples that are still growing, given the impact of sex on the timing of the adolescent growth spurt. For example, weight is more strongly correlated with pubertal onset in females than males, so correlations of weight and height changes may vary by sex.[61] 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 percentile greater than the 85th at study entry, all medication findings remained significant despite the smaller sample size. Several of the associations between biometric growth predictors and auxologic outcomes weakened. However, the weakening was minimal except for the correlation between premedication z-BMI and WRT entry. 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 percentile' preferentially impacted correlations with BMI change.[63]

The primary limitation of this observational analysis is that participants were not protected by randomization; we included all participants regularly using medication over any 6-month period during the study regardless of their initial randomized assignments to medication or nonmedication arms. Therefore, causal relationships between predictors and outcomes should not be assumed because it is possible that 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, 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.[13,14,17] 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 decreases may be more likely to occur before weight recovery efforts. Last, 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 decrease 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 vs switching to alternative treatments. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Methods of Blood Pressure Measurement in Neonates Have Evolved Over Time, But Need Further Evolution

Kirkland RT, Kirkland JL. Systolic blood pressure measurement in the newborn infant with the transcutaneous Doppler method. J Pediatr 1972;80:52-6.

Proper measurement of blood pressure (BP) values in newborns can be challenging, but is critically important in the neonatal intensive care unit. Both hypotension and hypertension can be associated with serious adverse outcomes. One of the difficulties of measurement is that the use of technology developed for adults may not be accurate within the expected lower BP range of neonates.

Kirkland and Kirkland, in 1972, describe their technique for using the Doppler ultrasound method of BP measurement in full-term newborns compared with the auscultation, palpation, and flush methods. They successfully measured systolic BP, but the values were higher than by the other methods. The auscultatory and palpation methods were often unsuccessful in the nursery setting. Additional observations included finding that BP increases over the first week of life, that higher BP values occur with a smaller cuff size, and that changes in the activity level of the infant caused substantial differences in the BP values.

The Doppler ultrasound method of BP measurement in neonates has largely been replaced by oscillometric measurement, although some clinicians with expertise in the Doppler method still use it. Oscillometric devices detect the pressure oscillations in the artery, with the maximal oscillation correlating with the mean arterial pressure (MAP). Compared with the gold standard method of intra-arterial BP monitoring, the MAP is more accurate than systolic or diastolic BP, but the SD of the measurements can be large and clinically significant.[1] In addition, the devices are less accurate when the MAP is 30 mmHg or less.

The International Neonatal Consortium in its systematic review of the literature on BP methods in neonates recommends that oscillometric devices can be used to screen for BP abnormalities, but if the device detects values that are too low, too high, or are inconsistent with the clinical picture of the infant, intra-arterial measurements be obtained.[1] They also recommend using a cuff size with a cuff width to arm circumference ratio of 50%, to use the right upper arm preferentially, and basing clinical decision-making on multiple measurements. So, although oscillometric devices have improved on the Doppler method because they do not need operator expertise, they remain inadequate for many neonates. An innovative BP device developed primarily for the lower BP ranges of neonates is desperately needed, hopefully without having to wait another 50 years.

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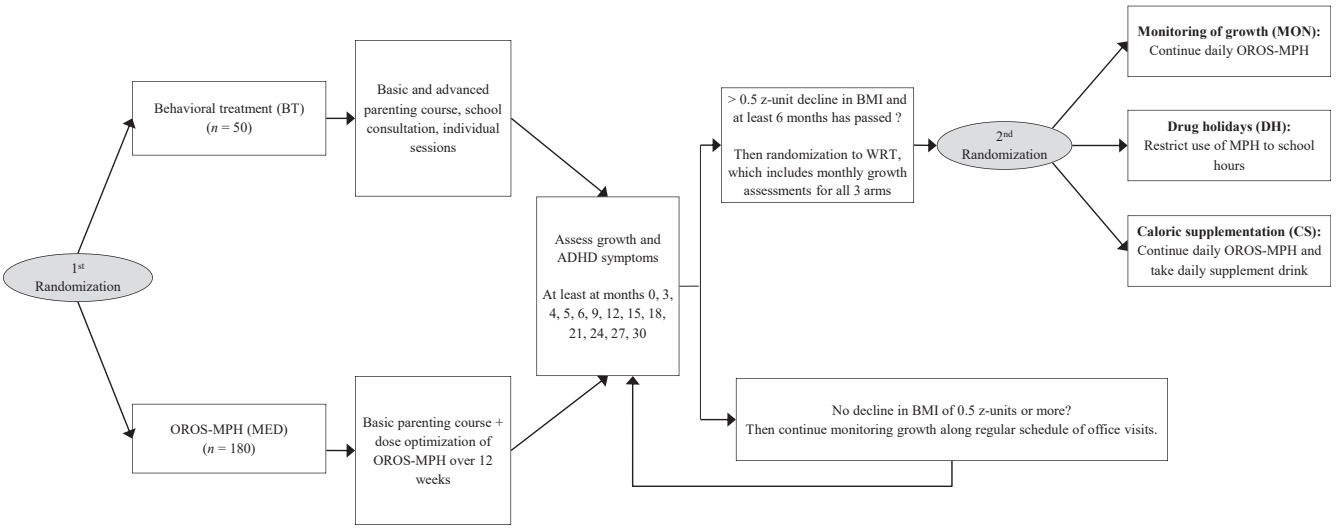

Figure 1. Study flowchart. Reprinted from "A Randomized Controlled Trial of Interventions for Growth Suppression in Children With Attention-Deficit/Hyperactivity Disorder Treated With Central Nervous System Stimulants," by J.G. Waxmonsky, 2020, *Journal of the American Academy of Child & Adolescent Psychiatry*, *59*, p. 1333. Copyright 2020 by the Elsevier. Reprinted with permission.

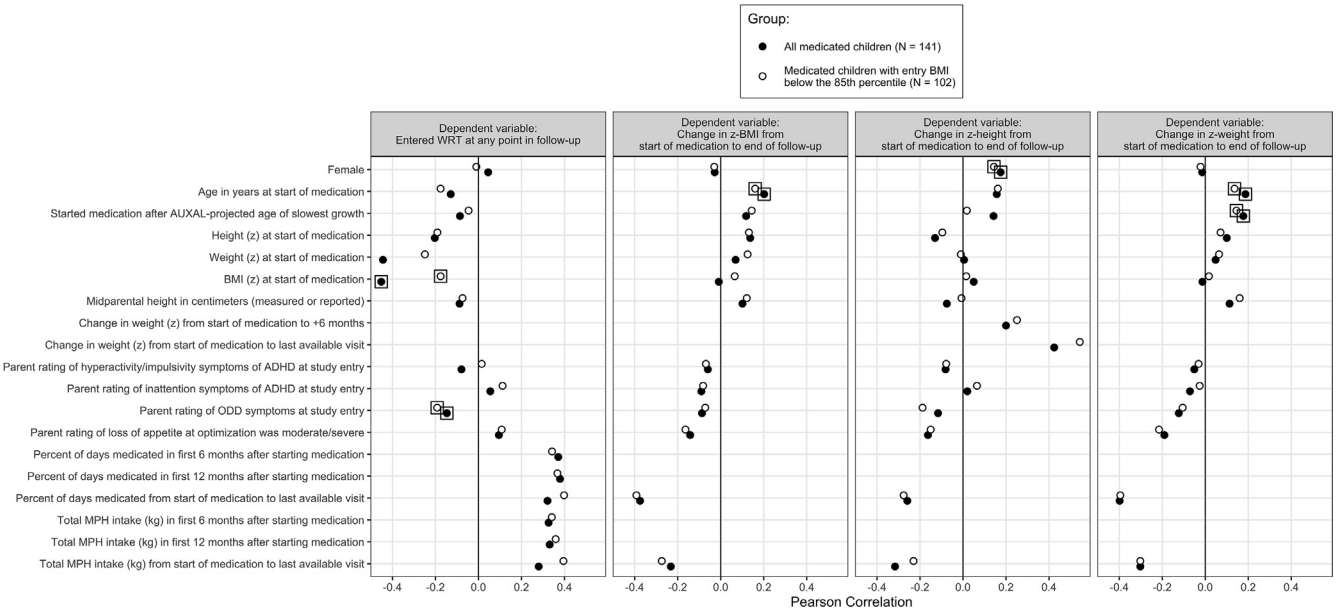

Figure 4. Sensitivity analysis 1: excluding children above the 85th percentile in BMI at study entry. Compares correlations based on all children who took medication (black circles) with correlations based on only those with entry BMI below the 85th percentile (white circles). Pairs of correlations with a box around them differed in statistical significance (ie, 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. *AUXAL*, structural auxologic analysis model.

Table II. Characteristics at study entry of those included vs excluded from analyses

Variables	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)

BA, Bachelor's degree; *CD*, conduct disorder.
Participants in the larger study were excluded from this analysis if they did not use medication for ≥6 months.
Number of ODD/CD symptoms is per parent report.
*$P < .05$.

Table IV. Correlates of entering WRT and changes in z-BMI, z-weight, and z-height in the first 12 months after starting MPH

	Δ z-BMI from 0 to 12 months		Δ z-weight from 0 to 12 months		Δ z-height from 0 to 12 months	
Predictors	Correlation (SE)	Sig.	Correlation (SE)	Sig.	Correlation (SE)	Sig.
Biometrics						
Female	−0.06 (0.09)		−0.09 (0.09)		+0.12 (0.09)	
Age at start of medication, years	+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)	*

AUXAL, structural auxologic analysis model.
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.
*$P < .05$.
†$P < .01$.
‡$P < .001$.