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A Randomized Controlled Trial of Interventions for Growth Suppression in Children With Attention-Deficit/Hyperactivity Disorder Treated With Central Nervous System Stimulants

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Objective: To examine the impact of central nervous system (CNS) stimulants on the growth of children with attention-deficit/hyperactivity disorder (ADHD), and to assess the efficacy and feasibility of weight recovery interventions on growth.

Method: A total of 230 children aged 5 to 12 years with ADHD with no history of chronic CNS stimulant use were randomly assigned to receive daily CNS stimulants (78%, primarily osmotic release oral system-methylphenidate [OROS-MPH]) or behavioral treatment (22%) for 30 months. After 6 months, children evidencing a decline in body mass index (BMI) of >0.5 *z*-units were randomized to 1 of 3 weight recovery treatments (WRTs): monthly monitoring of height/weight (MON) plus continued daily medication; drug holidays (DH) with medication limited to school days; or daily caloric supplementation (CS) with a 150-kcal supplement plus daily medication.

Results: Before WRT assignment, medication was associated with significant reductions in standardized weight and height (p values <.01). Adherence to CS and DH during WRT was high, with significant increases in daily caloric intake and decreases in weekly medication exposure (p values <.05). Across all WRT participants (n = 71), weight velocity increased significantly after WRT randomization ($\beta_2 = 0.271$, SE = 0.027, $p < .001$).When analyzed by what parents did (versus what they were assigned to), CS ($p < .01$) and DH ($p < .05$) increased weight velocity more than MON. No increase in height velocity was seen after randomization to any WRT. Over the entire study, WRT participants declined in standardized weight (−0.44 *z*-units) and height (−0.20 *z*-units).

Conclusion: Drug holidays, caloric supplementation, and increased monitoring all led to increased weight velocity in children taking CNS stimulants, but none led to increased height velocity.

Clinical trial registration information: Novel Approach to Stimulant Induced Weight Suppression and Its Impact on Growth; https://clinicaltrials.gov/; NCT01109849.

Key words: attention-deficit/hyperactivity disorder, growth, CNS stimulants

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Central nervous system (CNS) stimulants are a first-line treatment for attention-deficit/hyperactivity disorder (ADHD)[1] and one of the most commonly prescribed medications in children and adolescents.[2] They have a well-established safety profile, with anorexia and weight loss being two common side effects.[1,3-5] Given these side effects, there have been long-standing concerns about growth suppression with these medications.[6]

Initial studies of immediate-release stimulants failed to find evidence of sustained growth suppression, but the average duration of use was only a few years.[7] Although care guidelines differ about sequencing of nonpharmacological to pharmacological treatments, all recommend continuing pharmacological treatment when impairment worsens off medication.[1,5,8] Over the past three decades, there has been a substantial increase in the number of children using CNS stimulants, the use of extended-release medications, and the cumulative doses taken over the lifetime,[2,9-12] suggesting that the frequency and intensity of growth suppression may be greater than that observed in initial studies. In the

National Institutes of Health–funded Multimodal Treatment of ADHD (MTA) study, growth rates declined during the first 2 years of treatment, then stabilized but did not accelerate in those participants continuing medication.[13] In adulthood, consistently medicated participants were approximately one inch shorter than unmedicated participants and a half-inch shorter than age-matched controls.[9]

Drug holidays, or temporary breaks from medication, are commonly used to improve the tolerability of CNS stimulants.[5,7,14] In the MTA, children inconsistently taking CNS stimulants were almost 1 inch taller as adults than those consistently taking medication.[9] However, MTA inconsistent users included children permanently stopping medication and those taking temporary breaks, with wide variation in the timing and intensity of medication exposure across participants. Therefore, the impact of prescribed drug holidays was not evaluated by the MTA. No prior work has randomly assigned children with documented growth suppression to continuous versus interrupted dosing to evaluate impacts on growth.

Other interventions for promoting growth in children taking CNS stimulants include (1) increased monitoring of growth and (2) improving caloric intake. The latter intervention is based on the premise that negative caloric balance may cause growth suppression with CNS stimulants.[15,16] However, there has been even less assessment of these interventions.[17]

To address limitations of previous research, we recruited 230 treatment-naive youths with ADHD and randomly assigned them to CNS stimulant medication (MED) or behavior therapy (BT). After at least 6 months of treatment, those showing sustained body mass index (BMI) declines were re-randomized to one of three weight recovery treatments (WRT): drug holidays (DH), caloric supplementation (CS), or the control of monthly monitoring (MON) of height and weight. We hypothesized the following: (1) that children treated with CNS stimulants would exhibit reduced growth compared to those not receiving medication; (2) that DH and CS would lead to increased weight gain; and (3) that only DH would be associated with accelerated height growth.

METHOD

Participants

Participants were 230 children 5 to 12 years of age meeting criteria for any *DSM-IV* ADHD subtype and using CNS stimulant medication under 30 days lifetime (unlikely to affect growth). The study was approved by the governing institutional review board. Parents gave written consent, and children gave assent. Exclusion criteria included IQ <70, obesity or BMI below the 5th percentile, use of other psychotropics or any medication/supplement found to increase height/weight, autism spectrum disorder, or milk protein allergies. Participants were recruited through mailings to schools, medical providers. and community mental health providers. ADHD was diagnosed using the Disruptive Behavior Disorders Structured Interview, administered by masters-level or higher clinicians,[18] combined with parent and teacher ratings.[19] Psychiatric comorbidity was assessed by the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children IV, computerized version,[20] with comorbid diagnoses allowed if ADHD was the most impairing condition. Diagnoses were confirmed by two MD/PhD faculty members.

ADHD Treatment Conditions

At baseline, families were randomly assigned to either medication (MED) or behavior therapy (BT) in a 4 to 1 ratio. This lead-in phase was used to ensure that only children manifesting measurable changes in weight and height entered WRT, with BT used as an active control, as ADHD itself is associated with altered growth.[13,15,21-23] Children in MED were initially treated with osmotic release oral system-methylphenidate (OROS-MPH), with dose titrated every 2 weeks until optimized. Treatment efficacy and tolerability were assessed by parent and teacher ratings.[24-26] Study physicians completed the Clinical Global Impressions Scale for Improvement and Severity (CGI-I, CGI-S)[27] at each visit. Optimal dose was defined as a tolerable dose at which participants achieved a level of home/school functioning that left no meaningful room for improvement. If OROS-MPH was not efficacious or tolerated, alternative MPH or amphetamine products were prescribed.

In BT, participants received an 8-week parenting program,[28] social skills groups, and ongoing school consultation, with additional treatment individualized as needed. Families in MED were offered the 8-week parenting program and one annual school consultation to incentivize enrollment.

Study treatment lasted up to 30 months. After 6 months, BT participants displaying moderate impairment or worse (CGI-S >3), were allowed to initiate medication to promote retention, as the study's primary goal was to measure growth, not treatment effects. All treatments were provided free of cost to participants.

Treatment Use

Participants were instructed to take study medication every day of the week. The numbers of pills dispensed and returned were recorded at each visit. Parents' recorded days medication were given in monthly logs. Logs and pill counts were synchronized at each visit. As in the MTA, medication

use was measured using total dosage (in milligrams) of methylphenidate equivalents.[9]

Height and Weight Measurements

Staff were trained and required to measure 10 adults and 10 children within 3 mm and 0.1 kg of the trainer. Children were measured wearing light clothing without footwear, using a standardized protocol on a calibrated, mounted stadiometer and digital scale. Weight was recorded to the nearest 0.1 kg and height to the nearest 0.1 cm. Measures were repeated three times, and the median value was used. Parent height was measured at baseline.

Assessment Schedule

Participants not using medication were assessed every 3 months. Participants using medication were seen monthly for 3 months after optimization and then at least every 3 months until study endpoint or until rerandomized to WRT. In WRT, assessments were completed monthly. At baseline and every visit after optimization, the child's food and beverage intake for the past 24 hours was collected using a standardized interview,[29] with caloric intake calculated using the Nutribase 2018 Pro edition.

Weight Recovery Treatment Conditions

Any time after 6 months, MED or BT (as BT-assigned youths could cross to medication after month 6) participants whose BMI *z* declined by $\geq$0.5 *z*-units (or $>$1 *z*-unit plus raw weight loss from baseline if entry BMI was $>$85th percentile) were randomized to 1 of 3 WRT arms: monitoring (MON), drug holiday (DH), or caloric supplementation (CS) (Figure 1). In all arms, dose increases were prohibited, and weight and height were measured monthly. In CS and MON, parents were advised to medicate daily. In DH, parents were told to medicate only on school days, and switched to either immediate-release MPH twice daily or MPH HCL extended-release capsules in effort to limit medication effects to school hours.[30] Participants with documented symptom worsening (CGI-S increasing by $\geq$1 point and score $\geq$4) could return to OROS-MPH on school days to ensure coverage for after-school activities. In CS, participants received an 8-oz, 150-kcal supplement drink to consume each evening (Nutripals; Abbott Laboratories, Abbott Park, Illinois). MON participants did not receive any treatments beyond monthly weight and height checks. WRT ended when participants returned to their baseline *z*-BMI score for two consecutive visits and were cleared by the study nutritionist to end WRT. Participants crossing two major weight or height for age percentile lines[31] (or falling below the 5th percentile) were assigned to additional active WRT arms until stabilized. If not sufficient, stimulant dose was incrementally lowered until height/weight percentile stabilized.

Data Analysis

As these analyses were designed to evaluate the impact of WRT, primary comparisons were among 3 groups: MON, DH, and CS (total n = 71).

Verification of Growth Suppression. We first verified that growth suppression occurred by comparing children entering WRT to participants never using medication during the study. For WRT participants, we computed change in height and weight from study baseline to WRT initiation**.** For participants who did not enter WRT, we computed change in height and weight from baseline to the visit nearest 10.7 months from baseline (ie, median time between baseline and WRT initiation for those in WRT). We then tested the statistical significance of the change for WRT versus never-medicated participants by using permutation tests.

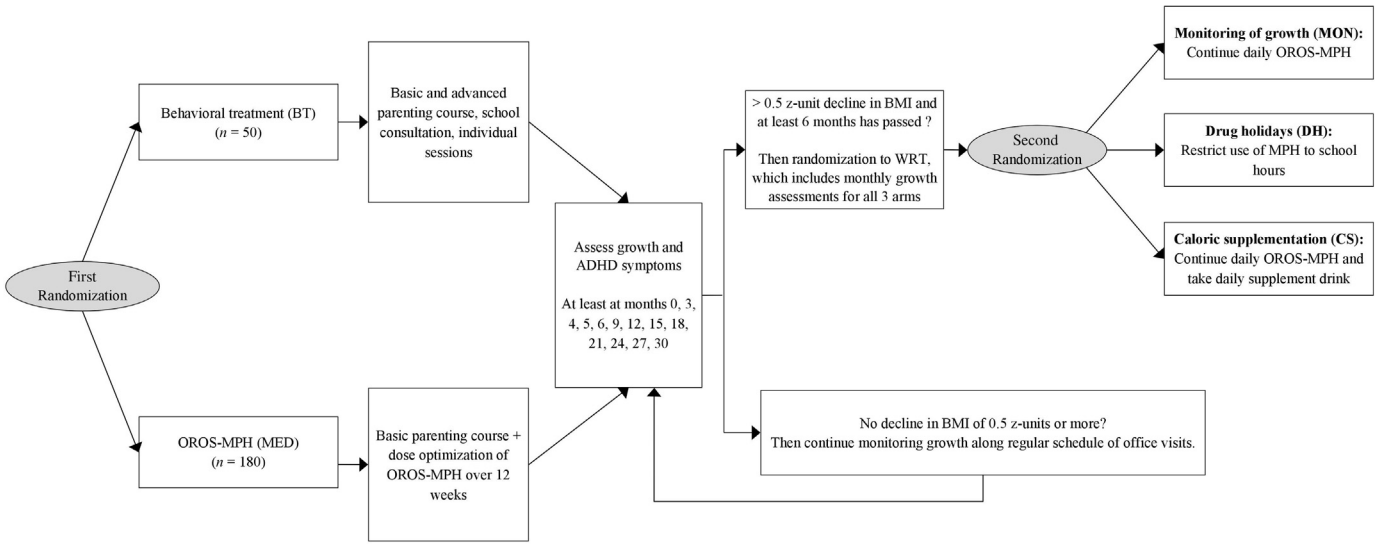
Timeframe of Growth Measurements. Time was scaled in months and centered at WRT initiation (ie, time = 0 at randomization). Measurements were filtered to include only those within 10 months of WRT initiation (before or after). The 10-month window was selected to restrict post-randomization follow-up to a time range in which there were few missing observations and to define a time interval in which growth could reasonably be modeled as linear.

Covariates. Four time-invariant covariates were included in growth models: age at randomization to WRT, female (0/1), age-by-female interaction, and mother's height. One binary, time-varying covariate was created using structural auxological analysis (AUXAL) to project the age of minimal growth velocity to address the large variation in the timing of puberty between children that cannot be accounted through *z*-scores.[32] Growth measurements before this time point were considered prepubertal. This covariate equaled 1 whenever a measurement occurred after that child's AUXAL-projected age of minimal growth velocity. AUXAL projections were based only on measurements prior to WRT randomization.

WRT Group Membership. For intent-to-treat (ITT) analyses, dummy variables indicated randomization to DH and CS, with MON as the reference group. Ten cases were prohibited from randomization to MON because they had a BMI $<$10th percentile at WRT entry (a feature of the safety protocol)—another dummy variable indicated whether randomization was restricted.

For per protocol (PP) analyses, dummy variables indicated membership in DH and CS, with MON as the

FIGURE 1 Study Flowchart



Note: *ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; OROS-MPH = osmotic release oral system methylphenidate; WRT = weight recovery treatments.*

reference group. Per protocol group membership was determined via review of calorie and medication logs. DH was defined as using medication >50% of weekends pre-WRT and <50% during WRT, with at least a 25% decline in use pre- to post-WRT. CS was defined as using supplement >50% of WRT days. MON was defined as not meeting criteria for DH or CS.

Growth Modeling. We fit multilevel spline models[33] in Mplus 7.4[34] to model participants' growth 10 months before and 10 months after WRT randomization. Repeated measurements of weight or height were nested within children. Time-invariant covariates included child age, child sex, the interaction of age and sex, and maternal *z*-height. A time-varying covariate indicated whether the child was prepubertal at each measurement. Three random effects comprised the child's growth curve: β_{0i}, β_{1i}, and β_{2i}. Parameter β_{0i} estimated the child's weight or height at WRT randomization (ie, in kilograms or centimeters). Parameter β_{1i} estimated the child's growth rate in the 10 months prior to WRT randomization (ie, kilograms per month or centimeters per month). Finally, parameter β_{2i} estimated the child's change in growth rate at WRT randomization (ie, change in kilograms per month or centimeters per month). Contrast coding was used to compare β_2 in MON versus DH versus CS. These contrasts evaluate the key question: whether the change in growth velocity at randomization to WRT differed among the WRT groups. Additional details on model specification and contrast procedure are provided in Supplement 1: Parameterization of Multilevel Growth Models, available online. A separate model was fit for each combination of outcomes (height versus weight) and treatment group definition (intent-to-treat versus per protocol). Missing data in covariates was minimal and was addressed using multiple imputation (see Supplement 2: Handling of Missing Data, available online).

RESULTS

The sample's mean age was 7.6 years and most were male participants, consistent with the MTA.[13] Most participants were of Hispanic ethnicity, with 11% having parents whose primary language was not English (see Table S1, available online). Only 5 participants (2.1%) previously used any CNS stimulants. All 230 participants were randomized, with 180 to MED and 50 to BT as planned (see Figure S1, available online). There were 143 MED and 24 BT participants dispensed any study medication, with 165 verified as taking at least 1 dose. There were 72 (44%) medication users entering WRT. One WRT participant originally assigned to BT never used medication (low entry BMI) and so was excluded from subsequent WRT analyses, leaving 71 medication-using participants for growth modeling (65 from MED, 6 from BT).

Rates of Weight and Height Growth Prior to WRT

To verify that WRT participants experienced a reduction in growth before entering WRT, we compared them to non-WRT participants never using medication with at least 12 months of data (n = 40). At study entry, WRT participants

were more impaired (means of 4.56 versus 5.01, $p < .05$), lighter (baseline difference of 0.38 *z*-units), shorter (difference of 0.25 *z*-units), and had a lower BMI (difference of 0.38 *z*-units) versus never-medicated participants, with no other significant differences. After adjusting for differences in standardized height and weight at study entry, WRT participants exhibited a significant change in standardized height ($p < .01$) and weight ($p < .01$) versus never-medicated participants (Figure 2) from study entry to WRT entry (see Supplement 3: How Growth of Children in WRT and Never Medicated Children Was Compared, available online). Between-group differences would amount to 0.66 cm and 3.7 kg over 1 year (see Supplement 4: How Values Were Translated Between Raw Height and Weight and *z*-Scores, available online).

WRT Assignment

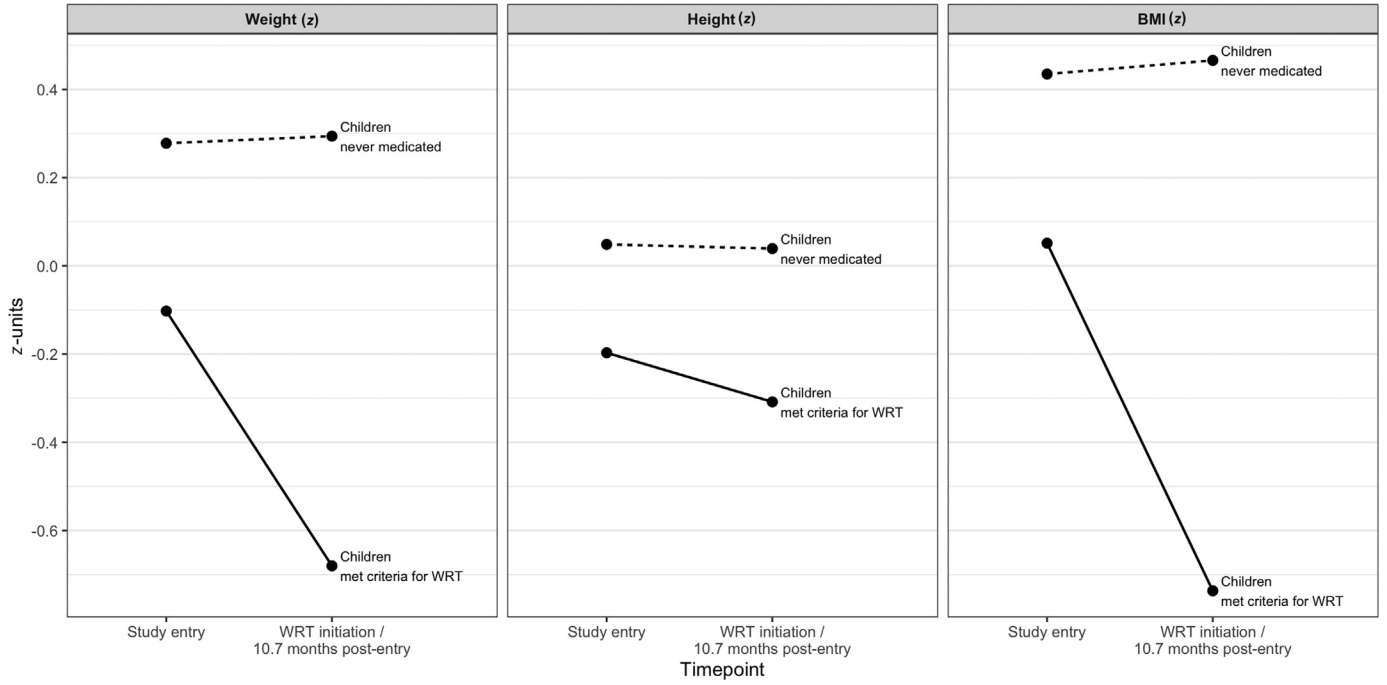
Of the 71 medicated participants entering WRT, 24 were randomized to CS, 24 to MON, and 23 to DH. Table 1 compares groups at WRT randomization. The mean time from study entry to WRT initiation was 12.7 months (SD = 6.4), with 18.3 months (SD = 6.5) from WRT initiation to WRT exit. WRT participants had an average of 22.7 (4.99) growth assessments, with 10.9 (5.5) occurring during WRT. There were 5 participants (7%) who discontinued the study while in WRT. Thirteen participants (18%) met criteria to exit WRT, having a mean WRT duration of 15.0 (range, 7.6−22.2) months. WRT completers' mean change in measurements during WRT were as follows: *z*-height, −0.20 units; *z*-weight, +0.45 units; and *z*-BMI, +0.82 units.

In DH, 105 WRT days occurred during summer break, amounting to 1.5 summers off medication based on school schedules. Within DH, 7 participants (30%) were maintained on the school-hours only regimen, with 16 (70%) reverting back to school-day use of OROS-MPH because of worsening ADHD symptoms after school. Seven participants (9.7%) needed additional WRT assignments to stabilize BMI, with one participant needing to be removed from medication to gain weight.

Medication Use

Intent-to-Treat. As intended, DH participants were medicated for fewer WRT days than CS or MON ($p < .05$). Both MON and DH had significant reductions in percentage of medicated days from pre-WRT to during WRT (MON: 82% to 69%, DH: 75% to 53%, p values $<.05$), with most unmedicated days occurring on weekends. Adherence to weekend holidays in DH was high, as parents gave medication on only 5% of weekend days (Figure 3A and see Table S2, available online). WRT participants' mean MPH dose when medicated was 24.3 mg (SD = 6.6), for a weight-adjusted dose of 0.97 mg/kg per day at WRT

FIGURE 2 Pre-Weight Recovery Treatments (WRT) Growth Velocity in Never-Medicated Children vs Eventual WRT Participants



Note: *For children who eventually entered WRT, median time between study entry and WRT initiation was 10.7 months. For children who were never medicated, the visit closest to 10.7 months after study entry was used for comparison.*

TABLE 1 Growth Measurements at Randomization to Weight Recovery Treatment (WRT)

		WRT group		
Analysis	**Measurement**	**Monitoring**	**Drug holiday**	**Caloric supplementation**
Intent-to-treat	Participant *z*-height	−0.07 (0.66)	−0.59 (1.00)	−0.28 (0.85)
	Maternal *z*-height	−0.03 (0.46)	−0.42 (0.47)	−0.01 (0.61)
	Participant *z*-weight	−0.37 (0.55)	−1.01 (0.97)	−0.67 (0.83)
	Participant *z*-BMI	−0.47 (0.58)	−0.99 (0.84)	−0.75 (0.74)
Per protocol	Participant *z*-height	−0.22 (0.78)	−0.57 (0.96)	−0.24 (0.88)
	Maternal *z*-height	−0.16 (0.48)	−0.35 (0.52)	−0.00 (0.62)
	Participant *z*-weight	−0.51 (0.66)	−1.04 (0.97)	−0.64 (0.86)
	Participant *z*-BMI	−0.57 (0.61)	−1.05 (0.91)	−0.74 (0.75)

Note: Maternal z-height collected at baseline visit. Participant measurements from visit at which child was randomized to one of three WRT groups. When groups are defined per protocol, differences between monitoring and drug holiday groups is statistically significant for participant z-weight and participant z-BMI (p < .10). BMI = body mass index.

entry and a mean cumulative exposure of 14,188 mg over the entire study (see Table S3, available online).

Per Protocol. Using per protocol classification, there were 17 participants in DH, 24 in CS, and 30 in MON. The primary switch from ITT to PP was reclassification from DH to MON due to weekend use not declining sufficiently because of low pre-WRT levels of weekend use. Per protocol, DH included 117 summer days, equating to 1.70 summers off medication. Unlike ITT, only DH (90% versus 54%, $p < .05$) significantly decreased the percentage of days medicated from before to during WRT (see Figure S2A and Table S2, available online).

Supplement Use and Calorie Intake

Intent-to-Treat. Mean caloric intake on medicated weekdays changed from pre-WRT to during WRT by +7% for DH (not significant), +14% for MON (not significant), and +20% for CS ($p < .05$) (Figure 3A). In CS, supplement was taken 78% of days (82% of medicated and 64% of unmedicated days).

Per Protocol. Mean caloric intake on medicated weekdays changed from pre-WRT to during WRT by −1% for DH (not significant), +18% for MON ($p < .05$), and +21% for CS ($p < .05$) (see Figure S2A, available online). In CS, supplement was taken 81% of days (85% of medicated and 66% of unmedicated days).

Impact of WRT on Weight

Estimated growth curves are displayed in Figure 3B. Growth parameters are reported in Table 2. Across all WRT participants (n = 71), weight velocity increased significantly after WRT randomization ($\beta_2 = 0.271$, SE = 0.027, $p < .001$). Neither *z*-height nor *z*-weight at study or WRT entry significantly correlated with *z*-weight change during WRT.

Intent-to-Treat. All WRT groups gained significantly more weight ($p < .001$) than they would have if they had continued their prerandomization trajectory (Table 2): MON (an additional 2.3 kg), DH (an additional 2.8 kg), and CS (an additional 2.9 kg) (see Supplement 5: How WRT Effect Sizes Were Calculated, available online). All groups displayed a marked increase in weight velocity after WRT initiation (ie, the growth curves inflect at WRT randomization) (Figure 3B). There were no significant between-group differences in weight velocity after WRT initiation.

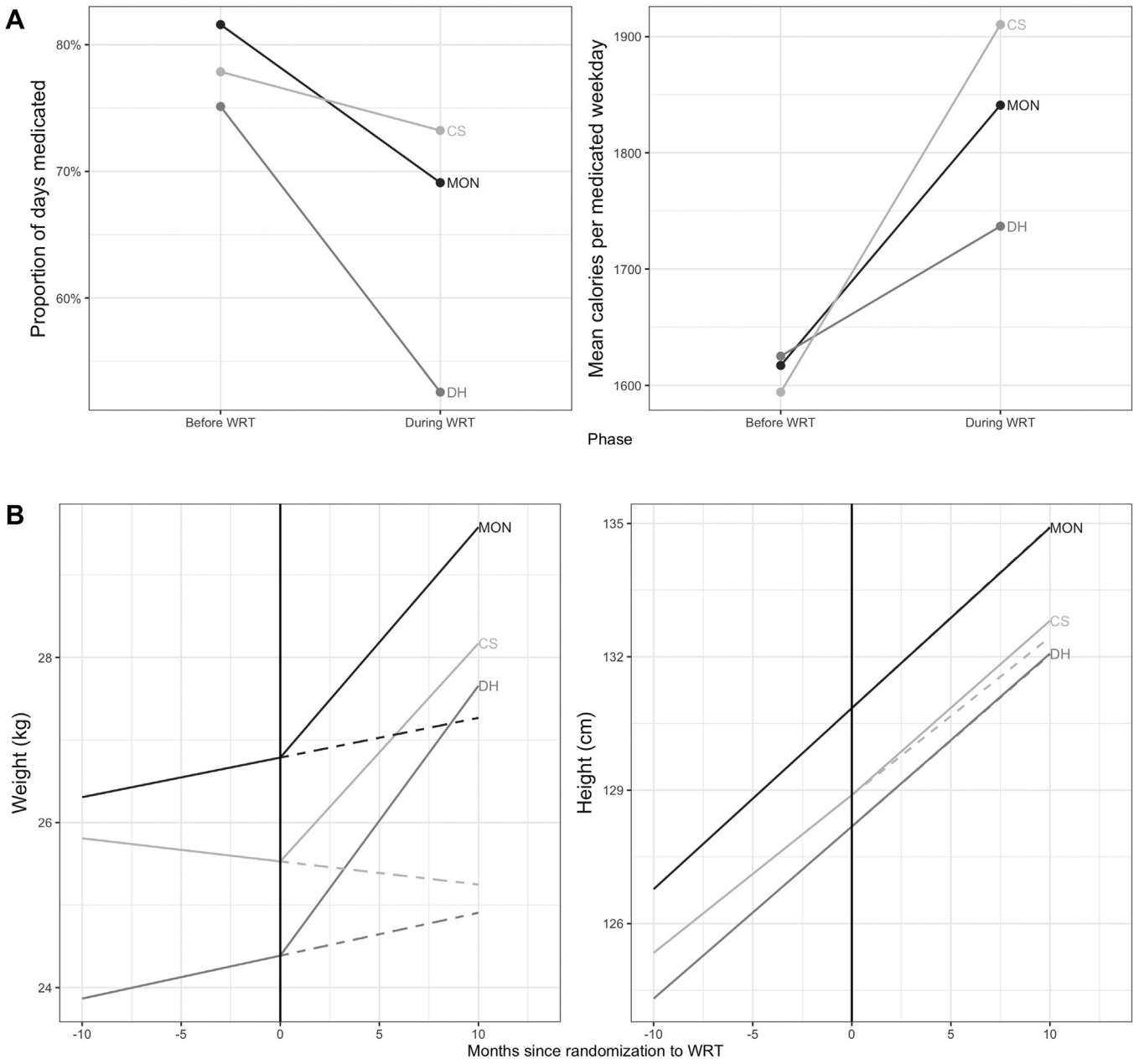
Per Protocol. All WRT groups gained significantly more weight over 10 months ($p < .001$) than they would have had they continued their prerandomization trajectory: MON (an additional 1.8 kg), DH (an additional 3.4 kg), and CS (an additional 3.0 kg) (Table 2). In contrast to intent-to-treat results, DH ($p < .05$) and CS ($p < .05$) increased weight velocity significantly more than MON (see Figure S2B, available online). Over the 10-month WRT randomization assessment period, a child classified as DH would be expected to gain 1.6 kg more than if that child had been classified as MON, and a child classified as CS would be expected to gain 1.2 kg more than a child in MON.

Impact of WRT on Height

Across all WRT participants (n = 71), there was no significant change in height velocity before versus after WRT randomization ($\beta_2 = 0.017$, SE = 0.019, not significant). Neither *z*-height nor *z*-weight at study or WRT entry significantly correlated with *z*-height change during WRT.

Intent-to-Treat. No WRT group significantly increased their height velocity, nor were there any statistically significant between-group differences. One effect size was nonnegligible: over the 10 months postrandomization WRT assessment period, children in CS gained 0.37 cm more than they would

FIGURE 3 Daily Exposures and Estimated Growth by Intent-to-Treat Weight Recovery Treatments (WRT) Group



Note: *(A) Curves are estimated growth for a male child aged 8.90 years with mother z-height of −0.13 (mean values of covariates). (B) Dashed lines show estimated growth, had child continued on pre-WRT trajectory. CS = caloric supplementation; DH = drug holiday; MON = increased monitoring of weight.*

TABLE 2 Estimated Growth Parameters

			Growth parameter				
Analysis	**Metric**	**Group**	**β_0 Intercept**	**β_1 Growth per month before randomization to WRT**	**β_2 Change in growth per month after randomization to WRT**	**Significant between-group differences in β_1**	**Significant between-group differences in β_2**
Intent-to-treat	Weight (kg)	Monitoring	26.8 (0.8) ***	+0.048 (0.035)	+0.231 (0.036) ***	None	None
		Drug holiday	24.4 (0.8) ***	+0.052 (0.033)	+0.275 (0.056) ***		
		Caloric supplement	25.5 (0.6) ***	−0.028 (0.034)	+0.292 (0.050) ***		
	Height (cm)	Monitoring	130.8 (1.0) ***	+0.407 (0.020) ***	−0.001 (0.032)	None	None
		Drug holiday	128.2 (1.3) ***	+0.387 (0.019) ***	+0.002 (0.028)		
		Caloric supplement	128.9 (1.0) ***	+0.355 (0.020) ***	+0.037 (0.031)		
Per protocol	Weight (kg)	Monitoring	25.9 (0.5) ***	+0.096 (0.026) ***	+0.181 (0.037) ***	MON > CS	MON < CS
		Drug holiday	25.1 (1.2) ***	−0.012 (0.027)	+0.337 (0.049) ***	MON > DH	MON < DH
		Caloric supplement	25.6 (0.7) ***	−0.043 (0.038)	+0.303 (0.049) ***		
	Height (cm)	Monitoring	129.8 (0.9) ***	+0.408 (0.018) ***	−0.006 (0.030)	None	None
		Drug holiday	129.0 (1.5) ***	+0.386 (0.022) ***	+0.011 (0.036)		
		Caloric supplement	129.1 (1.0) ***	+0.353 (0.020) ***	+0.043 (0.028)		

Note: *Intercept reflects estimated height or weight at randomization to weight recovery treatment. Estimates are those for a male child aged 8.90 years with mother z-height of −0.13 (mean values of covariates). CS = caloric supplement; DH = drug holiday; MON = monitoring.*

***$p < .001$.

have if they had continued their prerandomization trajectory. However, CS participants were growing more slowly than DH or MON before WRT ($p < .01$ for weight; $p < .10$ for height) (Table 2, Figure 3B). The increase brought CS only to a velocity comparable to that in the other WRT arms.

Per Protocol. When analyzed per protocol, results were largely unchanged (see Figure S2B, available online). Again, CS exceeded anticipated height gain by 0.43 cm, but this difference was not statistically significant.

Growth Trajectories Over the Entire Study

Estimating the magnitude of weight and height suppression associated with CNS stimulants was not the focus of this article but will be explored in future ones. A preliminary estimate can be derived from the mean change in standardized weight (−0.44 *z*-units) and height (−0.21 *z*-units) of the WRT group over the 30 months of assessment. This equates to 2.4 kg and 1.4 cm less versus expected values. Among children with at least 12 months of growth data, never-medicated youths had mean changes in standardized height and weight of +0.05 and +0.17 *z*-units respectively (equating to +0.3 cm and +0.9 kg), while youth who used study medication for at least 1 day but did not meet WRT criteria exhibited mean changes of –0.09 and –0.10 *z*-units respectively (equating to −0.6 cm and −0.6 kg) (see Table S3, available online).

Sensitivity Analyses

First, we extended the follow-up to 24 months after WRT randomization (see Table S4, available online), yielding results similar to those above. Second, we compared WRT groups using changes in standardized height and weight (versus growth models in the raw metric). From WRT entry to 10 months out, there were no differences between groups in changes in *z*-weight or *z*-height (see Table S5, available online). From WRT entry to WRT end, DH increased *z*-weight more than MON in intent-to-treat ($p < .10$) and per protocol ($p < .05$) analyses; there were no other significant between-group differences.

DISCUSSION

In 230 youths with ADHD, consistent versus no use of CNS stimulants was associated with significantly reduced weight and height velocity. Medicated participants exhibiting a sustained deficit in standardized BMI were then randomly assigned to one of three commonly used weight recovery treatments: increased growth monitoring (MON), drug holidays (DH), and caloric supplementation (CS). All groups significantly increased their rate of weight gain, but there were no significant between-group differences. When analyzed per protocol, DH and CS participants increased weight velocity significantly more than MON. Although DH significantly reduced MPH exposure and CS significantly increased caloric intake, no group increased in height velocity.

This was the first randomized ADHD trial designed to examine the impact of CNS stimulants, drug holidays, and caloric supplementation on weight and height. Previous ADHD studies were primarily chart reviews and post hoc analyses, with growth measured at irregular intervals using inconsistent methods. There were wide variations in participants' age, sex, and pubertal status that were often unaccounted for.[7,15,35-37] The MTA corrected many of these deficits and used an unmedicated ADHD comparison group, as ADHD itself may affect growth.[13,15,22,23] However, limitations remained. Approximately one-third of participants used medication prior to MTA entry, potentially confounding results.[38,39] Medication use was assessed retrospectively covering periods of up to 3 years, whereas growth was measured only 10 times spanning 16 years.[9] In contrast, more than 95% of our participants were stimulant naive. Medication use and caloric intake were tracked monthly during WRT with growth measured an average of 22 times in 3 years, and we accounted for variation in pubertal onset.

WRT increased weight gain with an impact similar to that seen in a trial of cyproheptadine.[17] Standardized weight did not return to premedication levels, potentially concerning for children underweight before starting medication. Prior work found that baseline weight/height predicts the degree of change in growth observed with medication.[15,40] We found no significant correlation between these parameters and changes during WRT. MON participants experienced the smallest increase; however, the change was clinically and statistically significant despite restrictions on what study providers could recommend versus the other arms or versus routine care. It appears that monthly weight checks may promote parents to adjust medication frequency and to increase calories.

It has been theorized that increasing weight or interrupting dosing would promote growth.[15,16] Despite significant changes in both, height velocity did not significantly increase for any group. Over the entire study, WRT participants grew 1.4 cm less than expected based on pre-WRT levels. Results are similar to what was observed for stimulant-naive youths who consistently used medication during the first 2 years of the MTA. The MTA defined consistent use as taking medication at least 50% of days,[9] so most WRT participants, even those in DH, would have been classified as consistent users. Other studies also observed that medication holidays affected weight but not

height.[35,36] Therefore, it appears that larger reductions in medication use beyond limiting it to only school days may be needed to meaningfully affect height velocity. Moreover, increasing weight velocity should be not be interpreted as sign of pending height rebound.

Medicated youths not meeting WRT criteria experienced smaller declines in standardized weight and height, suggesting that many medicated youths will not experience meaningful slowing in growth. The MTA and others found associations between adult height and total lifetime exposure to CNS stimulants.[9,41] Future work should assess for additional predisposing factors for growth suppression with CNS stimulants.

We did observe a nonsignificant increase in height velocity for CS participants during WRT. Pre-WRT, CS experienced the largest decline in weight velocity and were growing significantly more slowly than DH or MON. Past work has found that caloric supplementation leads to accelerated height in severely underweight children.[42,43] Therefore, it is possible that only children experiencing marked weight loss with CNS stimulants, which is relatively uncommon,[13] may exhibit increased height velocity with caloric supplementation.

Other reasons for failure to detect increased height velocity could include an insufficient intensity or duration of intervention, especially for DH. Reduced rates of weekend use before assignment to DH may have affected the ITT analysis, but per protocol analysis corrected for this and still found no evidence of growth acceleration. DH attempted to limit medication to school hours versus just school days by switching to shorter duration medications. Only 30% of DH participants continued on shorter-acting medications because of impairing symptoms after school. Therefore, if more intensive drug holidays are needed to increase growth, it seems that most families would not tolerate them. Prior work observed increased growth only during the second of two consecutive summers off medication versus that in children continuously treated.[37] However, that study did not account for group differences in age or timing of the pubertal growth spurt. No acceleration in height velocity was observed when we included all WRT assessment points (Table S3), totaling nearly two full summers, making it unlikely that insufficient duration was a factor. Results were similar when we examined standardized versus raw height (Table S4).

Adherence to weekend drug holidays was high. Parents were much more likely to deviate protocol by not giving weekend medication when asked to, even before weight loss was identified as a concern (ie, prior to WRT). Intermittent adherence is common for psychotropic medication, especially CNS stimulants on weekends.[44,45] Therefore, clinicians should assess current rates of weekend use before recommending drug holidays to improve tolerability. Results also demonstrate that some children may experience meaningful reductions in height and weight velocity even when not using medication daily.

Supplement adherence was also strong, with rates comparable to those in studies in nutritionally at-risk children and higher than that reported for cyproheptadine to increase weight in children with ADHD.[17,42] The randomly assigned CS group maintained their level of medication use post-randomization, whereas the MON group decreased use of their own accord. It may be that parents are more comfortable continuing ADHD medication when provided with an active intervention to address side effect concerns.

Although 30 months is long for a treatment trial, the primary limitation is study duration and lack adult outcomes. We completed a sensitivity analysis using all WRT time points through 24 months, with little change in results. However, it is still possible that treatment effects may have emerged after this time, or that larger samples may be necessary to detect treatment effects for growth. Associations between ADHD and BMI in medicated youths shift with age.[46] In the MTA, standardized BMI increased over adolescence regardless of medication use,[9] and ADHD is associated with obesity in adults.[47-49] Therefore, more intensive efforts to increase weight in childhood may not be advisable for many youths with ADHD.

Another major limitation was participants deviating protocol for medication administration. Although few parents gave medication when not assigned to, parents frequently reduced weekend medication use on their own. Future work should examine the role of parental preference about dosing schedules for improving adherence. Reduced weekend use prior to WRT in those subsequently assigned to DH and during WRT in MON (see Table S1, available online) may explain why the randomized arms did not show significant differences for weight velocity. When examined per protocol, DH and CS were superior to MON, albeit outside the inferential protection of randomization. Therefore, our capacity to say that these treatments increase weight gain more than frequent monitoring must be qualified by this limitation. For height, there were no substantial differences between ITT and per-protocol results.

Finally, design features may have altered the degree of growth suppression. Our threshold for initiating WRT was likely milder than that used in clinical practice, as our goal was to prevent growth suppression. The average MPH dose was below that in the MTA medication-only arm, likely due to limits on increasing dose during WRT and the availability of psychosocial treatments for all participants, which predicts less frequent dose changes.[50] However, our trial mimicked modern dosing practices with daily use of

extended-release stimulants,[1,5,8] whereas the MTA and other studies used immediate-release MPH.[37,38] We still observed significant weight and height suppression in the pre-WRT period. Lack of WRT effects on height were not due to failure to induce meaningful height suppression in the pre-WRT period.

In treatment-naive youths, CNS stimulants were associated with significantly reduced weight and height velocity. Increased monitoring of growth, drug holidays, and caloric supplements all significantly increased weight gain, with per protocol analysis showing larger effects for drug holidays and caloric supplementation. All treatments were tolerable except for switching to shorter-acting preparations during school days. Despite increasing weight velocity, no treatment increased height velocity. Therefore, in children taking CNS stimulants, it appears that limiting medication exposure to school days or increasing calories is not sufficient to meaningfully counteract the growth suppression observed with initiating CNS stimulants.

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REFERENCES

1. Pliszka S; Issues AWGoQ. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:894-921.
2. Hales CM, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents—United States, 1999-2014. JAMA. 2018;319:2009-2020.
3. Greenhill LL, Pliszka S, Dulcan MK, *et al*. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002;41(2 Suppl):26S-49S.
4. Cortese S, Holtmann M, Banaschewski T, *et al*. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry. 2013;54:227-246.
5. NICE. ADHD: diagnosis and management (NG87). NICE Guidelines. 2018. Available at:; nice.org.uk/guidance/ng87. Accessed July 5, 2018.
6. Safer D, Allen R, Barr E. Depression of growth in hyperactive children on stimulant drugs. N Engl J Med. 1972;287:217-220.
7. Ibrahim K, Donyai P. Drug holidays from ADHD medication: international experience over the past four decades. J Atten Disord. 2015;19:551-568.
8. Wolraich M, Brown L, Brown RT, *et al*. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128:1007-1022.
9. Swanson JM, Arnold LE, Molina BS, *et al*. Young adult outcomes in the follow-up of the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder: symptom persistence, source discrepancy, and height suppression. J Child Psychol Psychiatry. 2017;58:663-678.
10. Visser SN, Danielson ML, Bitsko RH, *et al*. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. J Am Acad Child Adolesc Psychiatry. 2014;53:34-46.e32.
11. Raman SR, Marshall SW, Gaynes BN, Haynes K, Naftel AJ, Stürmer T. An observational study of pharmacological treatment in primary care of children with ADHD in the United kingdom. Psychiatr Serv. 2015;66:617-624.
12. van den Ban E, Souverein PC, Swaab H, van Engeland H, Egberts TC, Heerdink ER. Less discontinuation of ADHD drug use since the availability of long-acting ADHD medication in children, adolescents and adults under the age of 45 years in the Netherlands. Atten Defic Hyperact Disord. 2010;2:213-220.
13. Swanson JM, Elliott GR, Greenhill LL, *et al*. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry. 2007;46:1015-1027.
14. van de Loo-Neus GH, Rommelse N, Buitelaar JK. To stop or not to stop? How long should medication treatment of attention-deficit hyperactivity disorder be extended? Eur Neuropsychopharmacol. 2011;21:584-599.
15. Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry. 2008;47:994-1009.
16. Poulton A. Growth on stimulant medication; clarifying the confusion: a review. Arch Dis Child. 2005;90:801-806.
17. Daviss WB, Scott J. A chart review of cyproheptadine for stimulant-induced weight loss. J Child Adolesc Psychopharmacol. 2004;14:65-73.
18. Hartung CM, McCarthy DM, Martin CA. Parent adolescent agreement on ADHD symptoms: a multi-trait, multi-methods model. J Psychopathol Behav Assess. 2005;27:159-168.
19. Pelham WE Jr, Gnagy EM, Greenslade KE, Milich R. Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. J Am Acad Child Adolesc Psychiatry. 1992;31:210-218.
20. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry. 2000;39:28-38.
21. Ptacek R, Kuzelova H, Paclt I, Zukov I, Fischer S. ADHD and growth: anthropometric changes in medicated and non-medicated ADHD boys. Med Sci Monit. 2009;15:CR595-599.
22. Hanć T, Cieślik J. Growth in stimulant-naive children with attention-deficit/hyperactivity disorder using cross-sectional and longitudinal approaches. Pediatrics. 2008;121:e967-e974.
23. Spencer T, Biederman J, Wilens T. Growth deficits in children with attention deficit hyperactivity disorder. Pediatrics. 1998;102:501-506.
24. Fabiano GA, Pelham WE Jr, Waschbusch DA, *et al*. A practical measure of impairment: psychometric properties of the impairment rating scale in samples of children with attention deficit hyperactivity disorder and two school-based samples. J Clin Child Adolesc Psychol. 2006;35:369-385.

25. Loney J, Millich R. Hyperactivity, inattention, and aggression in clinical practice. In: Wolraich M, Routh D, eds. Advances in Developmental and Behavioral Pediatrics, Vol 3. Greenwich, CT: JAI Press; 1982:113-147.
26. Pelham WE. Pharmacotherapy for children with ADHD. Sch Psychol Rev. 1993;22: 199-227.
27. Guy W. ECDEU Assessment Manual for Psychopharmacology. Washington, DC: US Dept of Health, Education and Welfare; 1976.
28. Cunningham CE, Brenner R, Secord-Gilbert M. The Community Parent Education Program (COPE): a school based family systems oriented course for parents of children with disruptive behavior disorders. Hamilton, ON: Canada: Chedoke-McMaster Hospitals and McMaster University; 1998.
29. Weber JL, Lytle L, Gittelsohn J, *et al*. Validity of self-reported dietary intake at school meals by American Indian children: the Pathways Study. J Am Diet Assoc. 2004;104: 746-752.
30. Swanson JM, Wigal SB, Wigal T, *et al*. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). Pediatrics. 2004;113: e206-e216.
31. Marchand V, Canadian Paediatric Society. The toddler who is falling off the growth chart. Paediatr Child Health. 2012;17:447-454.
32. Hermanusson M. Auxology: an update. Horm Res Pediatr. 2010;74:153-164.
33. Grimm K, Ram N, Estabrook R. Growth Modeling: Structural Equation and Multilevel Modeling Approaches. New York, NY: Guilford Press; 2016.
34. Muthen L, Muthen B. Mplus User's Guide, Seventh Edition. Los Angeles, CA: Muthen and Muthen; 2012.
35. Pliszka SR, Matthews TL, Braslow KJ, Watson MA. Comparative effects of methylphenidate and mixed salts amphetamine on height and weight in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45:520-526.
36. Satterfield JH, Cantwell DP, Schell A, Blaschke T. Growth of hyperactive children treated with methylphenidate. Arch Gen Psychiatry. 1979;36:212-217.
37. Klein RG, Landa B, Mattes JA, Klein DF. Methylphenidate and growth in hyperactive children. A controlled withdrawal study. Arch Gen Psychiatry. 1988;45: 1127-1130.
38. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56:1073-1086.
39. Poulton AS, Nanan R. Prior treatment with stimulant medication: a much neglected confounder of studies of growth in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2008;18:385-387.
40. Landgren M, Nasic S, Johnson M, Lövoll T, Holmgren D, Fernell E. Blood pressure and anthropometry in children treated with stimulants: a longitudinal cohort study with an individual approach. Neuropsychiatr Dis Treat. 2017;13:499-506.
41. Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years: adherence, effectiveness, and adverse effects. J Am Acad Child Adolesc Psychiatry. 2004;43:559-567.
42. Huynh DT, Estorninos E, Capeding MR, Oliver JS, Low YL, Rosales FJ. Impact of long-term use of oral nutritional supplement on nutritional adequacy, dietary diversity, food intake and growth of Filipino preschool children. J Nutr Sci. 2016;5:e20.
43. Kabir I, Malek MA, Mazumder RN, Rahman MM, Mahalanabis D. Rapid catch-up growth of children fed a high-protein diet during convalescence from shigellosis. Am J Clin Nutr. 1993;57:441-445.
44. Hack S, Chow B. Pediatric psychotropic medication compliance: a literature review and research-based suggestions for improving treatment compliance. J Child Adolesc Psychopharmacol. 2001;11:59-67.
45. Regnart J, McCartney J, Truter I. Drug holiday utilisation in ADHD-diagnosed children and adolescents in South Africa. J Child Adolesc Ment Health. 2014;26:95-107.
46. Waring ME, Lapane KL. Overweight in children and adolescents in relation to attention-deficit/hyperactivity disorder: results from a national sample. Pediatrics. 2008;122:e1-e6.
47. Cortese S, Ramos Olazagasti MA, Klein RG, Castellanos FX, Proal E, Mannuzza S. Obesity in men with childhood ADHD: a 33-year controlled, prospective, follow-up study. Pediatrics. 2013;131:e1731-1738.
48. Schwartz BS, Bailey-Davis L, Bandeen-Roche K, *et al*. Attention deficit disorder, stimulant use, and childhood body mass index trajectory. Pediatrics. 2014;133:668-676.
49. Hanć T. ADHD as a risk factor for obesity. Curr State Res. Psychiatr Pol. 2018;52: 309-322.
50. Vitiello B, Severe JB, Greenhill LL, *et al*. Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. J Am Acad Child Adolesc Psychiatry. 2001;40:188-196.