

## Stimulant-Related Reductions of Growth Rates in the PATS

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### ABSTRACT

**Objective:** To investigate growth of children with attention-deficit/hyperactivity disorder (ADHD) in the Preschool ADHD Treatment Study (PATS) before and after initiation of treatment with methylphenidate at titrated doses (average, 14.2 mg/day) administered three times daily, 7 days/week for  $\approx$ 1 year. **Method:** The heights and weights of 140 children with ADHD were measured up to 29 times in the PATS protocol, starting at an average age of 4.4 years. The relationship between standard (z) scores and time on medication was examined using mixed-effect regression to estimate change in relative size (slope). **Results:** Average relative size at baseline was significantly ( $p < .0001$ ) greater than zero for z height (+0.45) and z weight (+0.78), indicating greater than expected height (by 2.04 cm) and weight (by 1.78 kg). During treatment, slopes were significantly ( $p < .0001$ ) less than zero for z height ( $-0.304/\text{yr}$ ) and z weight ( $-0.530/\text{yr}$ ), indicating reduction of growth rates. For 95 children who remained on medication, annual growth rates were 20.3% less than expected for height ( $5.41 \text{ cm/yr} - 6.79 \text{ cm/yr} = -1.38 \text{ cm/yr}$ ) and 55.2% for weight ( $1.07 \text{ kg/yr} - 2.39 \text{ kg/yr} = -1.32 \text{ kg/yr}$ ). **Conclusions:** Risks of reduced growth rates should be balanced against expected benefits when preschool-age children are treated with stimulant medication. *J. Am. Acad. Child Adolesc. Psychiatry*, 2006;45(11):1304–1313. **Key Words:** attention-deficit/hyperactivity disorder, growth, stimulant medication.

The Preschool ADHD Treatment Study (PATS) was designed to provide information about the most commonly prescribed stimulant methylphenidate (MPH) when used to treat children younger than 5 years of age, for which little information from

controlled trials is available in the literature (see Greenhill et al., 2006). Reports of the general findings of the PATS are provided by Greenhill et al. (about efficacy) and by Wigal et al. (about safety) in this issue of the *Journal*. This report addresses the

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controversial area of effects of stimulant medication on physical growth.

The hypothesis of stimulant-related reduction in growth rates was proposed more than 3 decades ago (Safer et al., 1972), and current product labels and some modern guidelines (American Academy of Child and Adolescent Psychiatry, 2002) recommend regular monitoring of growth in children treated with stimulant medication. Multiple reviews of the literature on this topic are available (see Joshi, 2002; Kramer et al., 2000; Roche et al., 1979; Spencer et al., 1998), so another is not necessary here. When the PATS was initiated, a strong consensus was that the treatment of prepubertal children with stimulant medication may result in temporary slowing of growth but would not have an effect on adult size (National Institutes of Health Consensus Conference, 2000). This consensus was based on two hypotheses: the growth rebound hypothesis and the delayed maturation hypothesis. Safer et al. (1975) proposed that an initial stimulant-related reduction in growth rate would be offset by growth rebound (an increase compared to the pretreatment growth rate) when medication was stopped, and Satterfield et al. (1979) extended this hypothesis and proposed that growth rebound would occur even when medication was continued. Spencer et al. (1996) proposed a disorder-related delay in maturation characterized children with ADHD and may be mistaken as stimulant-related reduction in growth rate because most cases are treated with medication, and that late maturation results in growth catch up whether treatment with medication occurs or not.

The studies that have attempted to test these hypotheses have been inadequate because of methodological issues, including small sample sizes, outdated diagnostic criteria, cross-sectional designs and analyses, prior treatments with stimulants, lower than optimal doses, noncontinuous treatments, and inadequate control groups. Also, recent studies of short-term growth suppression in school-age children and adolescents have been inconsistent: some (see Lisska and Rivkees, 2003; MTA Group, 2004; Poulton and Cowell, 2003) have documented initial stimulant-related reductions in growth rates, but others have not (see Biederman et al., 2003; Pliszka et al., 2006).

In the face of uncertainty in the literature, the purpose of this report is to evaluate and describe the presence and magnitude of short-term stimulant-related growth

suppression in the youngest group of children currently treated with stimulants in clinical practice (preschool-age children with ADHD), for which little or no information is available. This may be the age group most affected if growth rates were suppressed by initiating treatment with stimulant medication during this early stage of development.

## METHOD

### Study Design

Detailed descriptions of the PATS entry criteria and the PATS methods are provided by Greenhill et al. and Kollins et al., respectively (2006), therefore, only brief summaries are presented here. After receiving written and verbal explanations of the PATS, parents provided written consent for their child's participation in the seven phases of the protocol addressed here: (1) screening, (2) pretreatment with a 10-week Community Parent Education program (Cunningham and Boyle, 2002; Cunningham et al., 1995), (3) baseline, (4) a 3-week lead-in trial on a range of potential doses (1.25–7.5 mg), (5) a 5-week, double-blind titration trial to select the best dose, (6) a 4-week double-blind comparison of groups randomized to the best regimen of MPH or placebo, and (7) 10-month maintenance treatment with clinical adjustments in dose if required.

Growth rates of the 140 stimulant-naïve preschool-age children who entered the PATS protocol (see Greenhill et al., 2006) were evaluated. Subgroups of the children who completed the maintenance phase of the PATS (completers,  $n = 95$ ) and those who did not (noncompleters,  $n = 45$ ) were compared. The reasons for noncompletion are described in more detail by Greenhill et al. and Wigal et al. elsewhere in this issue.

### Growth Measurements

In the screening through maintenance phases of the PATS protocol, 29 assessment points were specified when height and weight could be measured (Table 1). These assessments cover two informative periods of the protocol: (1) a period when medication was not used that was necessary to qualify multiple participants to form a group for the Community Parent Education intervention and then to deliver this 10-week pretreatment (i.e., from the screening to the baseline assessment), and (2) a period when medication was administered and evaluated in multiple phases of the protocol (i.e., from the initial lead-in to the final maintenance assessment).

Research assistants followed simple instructions and used standard medical office procedures to measure height (in centimeters) and weight (in kilograms) of the participants without shoes or heavy clothes. Growth charts (Kuczmarski et al., 2000) provided by the Centers for Disease Control and Prevention (CDC) were used along with the accompanying formulas to transform the absolute units of measurement (centimeters and kilograms) into relative or SD units ( $z$  scores), which are psychometrically sound (see Spencer et al., 1996) and appropriate for use in statistical tests. The standard scores for height ( $z$  height) and weight ( $z$  weight) were specified as the primary outcome measures of this report. Absolute measures (centimeters and kilograms) and percentile scores, which are entered directly onto CDC growth charts and are used in clinical practice, were secondary outcome measures. Height and weight measures were systematically screened before analysis to identify mistakes and

**TABLE 1**  
Assessment Points in the Preschool ADHD Treatment Study Protocol

Visit No.	Average Days From Baseline	Phase of Protocol	Description of Components of Phases
1	-117	1	Screening (followed by 3- to 10-mo wait)
2	-30	2	Community Parent Education <sup>a</sup> (10 wk)
3	0	3	Baseline (first medication dispensed)
4	7	4	O1, open lead-in wk 1
5	14		O2, open lead-in wk 2
6	21		O3, open lead-in wk 3
7	28	5	T1, crossover titration, wk 1
8	35		T2, crossover titration, wk 2
9	42		T3, crossover titration, wk 3
10	49		T4, crossover titration, wk 4
11	56		T5, crossover titration, wk 5
12	63		T6, crossover titration, high dose, wk 6 <sup>a</sup>
13	70		T7, crossover titration, high dose, wk 7 <sup>a</sup>
14	74		Washout <sup>a</sup>
15	77	6	P1, parallel group phase, wk 1
16	84		P2, parallel group phase, wk 2
17	91		P3, parallel group phase, wk 3
18	98		P4, parallel group phase, wk 4
19	99		P-term, double-blind termination <sup>a</sup>
20	126	7	M1, open-label maintenance, mo 1
21	154		M2, open-label maintenance, mo 2
22	182		M3, open-label maintenance, mo 3
23	210		M4, open-label maintenance, mo 4
24	238		M5, open-label maintenance, mo 5
25	266		M6, open-label maintenance, mo 6
26	294		M7, open-label maintenance, mo 7
27	322		M8, open-label maintenance, mo 8
28	350		M9, open-label maintenance, mo 9
29	378		M10, open-label maintenance, mo 10

Note: O = open lead-in phase; T = titration phase; P = parallel group phase; M = open-label maintenance phase.

<sup>a</sup> Optional measures of growth.

outliers, as recommended when measurements of height and weight are made without specific training of staff or close monitoring of technique (Lipman et al., 2004; Ulijaszek and Kerr, 1999). This resulted in the removal of 15 data points (0.15%) for height and 19 data points (0.19%) for weight.

### Statistical Analysis

A mixed-effects regression model was used to evaluate the effect of time on medication (expressed as days or years) from the baseline assessment to the end of maintenance (EOM) assessment on relative size (expressed as *z* height and *z* weight). The EOM assessment was defined as point 29 (Table 1) for the completers and as the point of the last observation before being dropped from the protocol for the noncompleters. The mixed-effects regression allowed for variation across individuals in time on medication. Completion status with two levels (completers and noncompleters) and site with six levels

(the locations where the study was conducted) were included as fixed effects. The mixed-effects model provided regression equations with estimates of intercepts (initial relative size) and slopes (change in relative size over time) for each individual. Under the null hypotheses based on the assumptions of normal size at baseline and normal annual growth as defined by the CDC growth charts, the average values of the intercepts and slopes are expected to be zero.

In addition, paired *t* tests were used to evaluate the change in height and weight from the baseline assessment to the EOM assessment. For absolute measures of size (centimeters and kilograms), the difference between measures obtained at different times can be used to estimate growth velocity (Argyle, 2003). For each individual, the baseline-EOM differences were divided by the number of days between the two assessments and then multiplied by 365 to provide the same time frame (annual) for estimates of growth rates (velocities). Norms (Kuczmarski, 2000) were used to specify expected size of the PATS sample at the average ages of the baseline assessment ( $\approx 4.75$  years) and the EOM assessment ( $\approx 5.75$  years), and the difference was used as the expected average annual growth rates (6.79 cm/yr and 2.39 kg/yr) based on the assumption of normal growth.

## RESULTS

### Screening and Baseline Growth Measurements

The data from the screening assessments, performed at an average age of 4.4 years, are shown in scatterplots (showing the degree of individual differences) of relative size versus time before baseline presented in the left sides of Figure 1A (for *z* height) and Figure 1B (for *z* weight). At the screening assessment, the average *z* scores (Table 2, column 1) were significantly different from zero for *z* height ( $t_{129} = 5.44, p < .0001$ ) and *z* weight ( $t_{128} = 9.33, p < .0001$ ) and were positive for *z* height (0.48) and *z* weight (0.77), indicating larger than expected relative size. At the baseline assessments, performed at an average age of 4.77 years, the average *z* scores (Table 2, column 2) were also significantly different than zero for *z* height ( $t_{133} = 5.64, p < .0001$ ) and for *z* weight ( $t_{132} = 9.24, p < .0001$ ). The estimates of average size of the PATS group at baseline (*z* height = 0.45 and *z* weight = 0.78) were close to those from the screening.

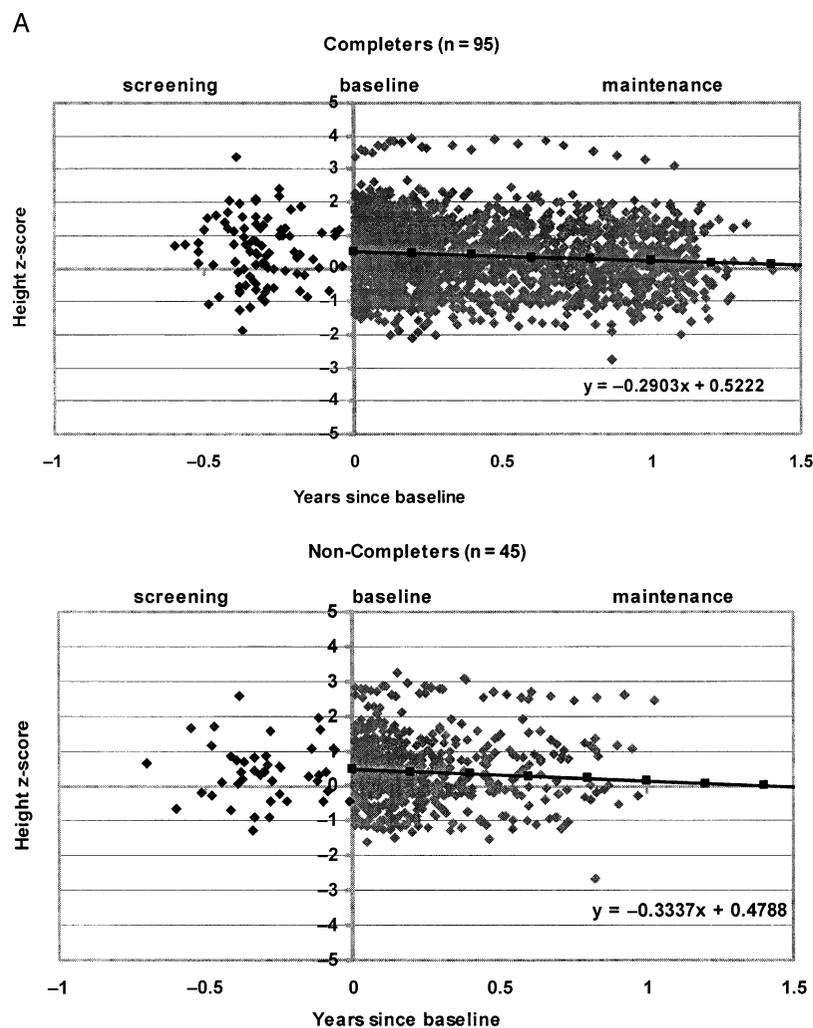
For children with measures at both assessment points, the screening-baseline differences for *z* height ( $t_{124} = -1.74, p = .08$ ) and for *z* weight ( $t_{121} = 0.68, p = .50$ ) were not statistically significant for the overall group or for the subgroups of completers for *z* height ( $t_{84} = -1.31, p = .19$ ) or for *z* weight ( $t_{83} = 0.10, p = .92$ ) or noncompleters for *z* height ( $t_{39} = 1.24, p = .22$ ) and for *z* weight ( $t_{37} = -0.93, p = .36$ ). Thus, before medication was initiated relative size was stable, and at baseline most of the participants had *z* scores  $>0$  (73.1% for height and 79.7% for weight), indicating larger than expected size compared to the current norms.

Based on averages at the 50th percentile (106.91 cm and 18.40 kg) and SDs (4.54 cm and 2.28 kg) derived from the CDC norms for children 4 years and 9 months of age,  $z$  score means were transformed to absolute measures to estimate how much taller (2.04 cm) and heavier (1.78 kg) than expected the PATS group was at the baseline assessment. The average body mass index for the group was 16.9, which corresponds to the 86th percentile at the baseline assessment (Table 2).

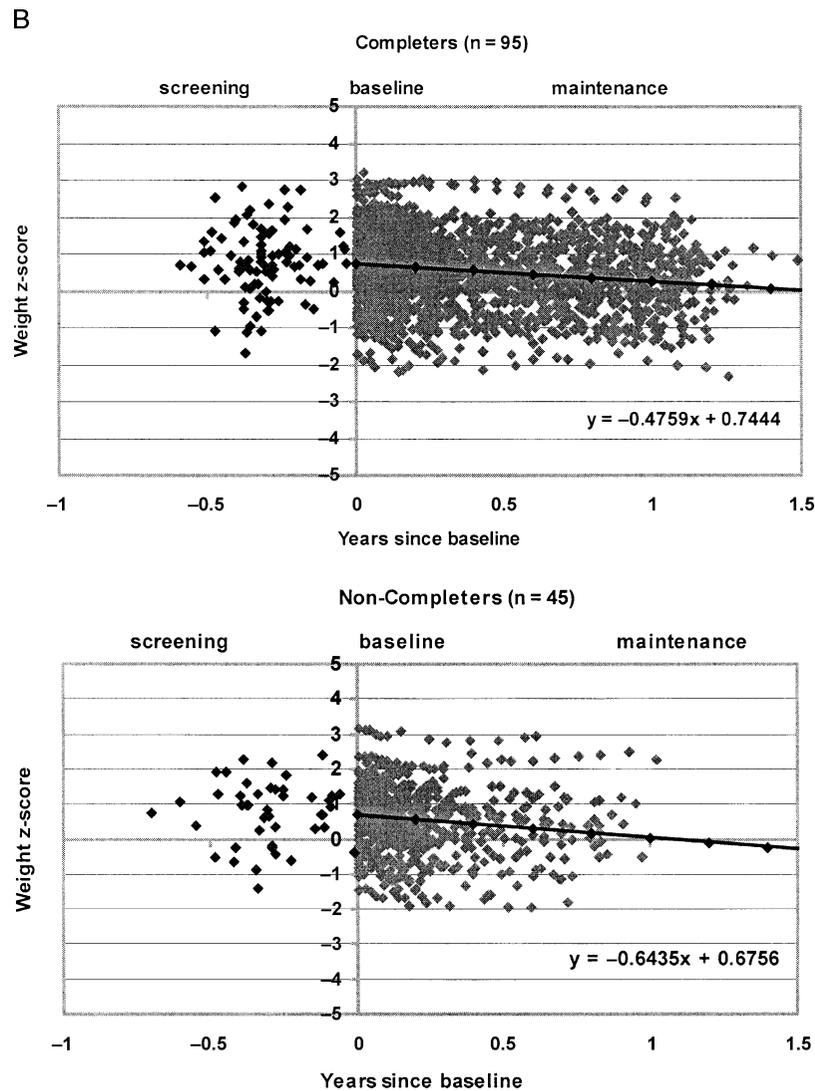
#### Changes in Growth Rates During MPH Treatment

The primary analyses to evaluate change in growth rates were based on the slopes of the mixed-effects regression equations relating relative size ( $z$  height and  $z$  weight) to time after baseline (expressed in days or

years). The scatterplots are shown on the right sides of Figure 1. Under the null hypotheses of normal growth rates, the slopes and intercepts are expected to be zero. In the mixed-effects regression analysis, the overall slopes were significantly different than zero for  $z$  height ( $t_{2,179} = -9.23, p < .0001$ ) and  $z$  weight ( $t_{2,208} = -13.54, p < .0001$ ) and were negative for  $z$  height ( $-0.312 \pm 0.041$ ) and  $z$  weight ( $0.560 \pm 0.046$ ), reflecting decreases in growth rates after initiation of pharmacological treatment with MPH. The intercepts were significantly different than zero for  $z$  height ( $t_{133} = 5.17, p < .0001$ ) and  $z$  weight ( $t_{133} = 7.59, p < .0001$ ) but were positive for  $z$  height ( $0.463 \pm 0.089$ ) and  $z$  weight ( $0.725 \pm 0.096$ ), confirming the larger than normal size before initiation of treatment with stimulant medication.



**Fig. 1** (A) Scatterplot of  $z$  height for completers ( $n = 95$ ) and noncompleters ( $n = 45$ ).



**Fig. 1** (B) Scatterplot of  $z$  weight for completers ( $n = 95$ ) and noncompleters ( $n = 45$ ).

The effect of completion status was not significant for height ( $t_{2,179} = 0.53, p = .5979$ ) or weight ( $t_{2,208} = 1.82, p = .0693$ ), because of similar subgroup values for the slopes (Fig. 1). The slopes were significantly different from zero for both the subgroup of 95 completers for  $z$  height ( $t_{2,179} = -8.81, p < .0001$ ) and  $z$  weight ( $t_{2,208} = -11.14, p < .0001$ ) and the subgroup of non-completers for  $z$  height ( $t_{2,179} = -4.43, p < .0001$ ) and  $z$  weight ( $t_{2,208} = -7.88, p < .0001$ ). The comparison of slopes revealed a surprising trend of more negative slopes for the noncompleters than the completers for both  $z$  height ( $-0.334 \pm 0.076$  vs  $-0.290 \pm 0.033$ ) and  $z$  weight ( $-0.644 \pm 0.082$  vs  $-0.476 \pm 0.043$ ). The addition of a quadratic term in a post hoc regression

analyses indicated that for the analysis of  $z$  weight (but not for  $z$  height) the quadratic component was significant and completion status interacted with time ( $t_{2,206} = 2.34, p < .0195$ ) because of a nonlinear temporal pattern of initial deceleration followed by acceleration that was greater for the noncompleters than for the completers.

To supplement the scatterplots presented in Figure 1, the group averages at the multiple assessment points were also calculated and graphed to provide a different view of the change in relative size over time. As shown in Figure 2, the group means for both  $z$  height and  $z$  weight were stable from the lead-in phase through the first few weeks of the titration phase, but then the group means declined over the time that the subgroups remained on medication,

TABLE 2

Absolute, *z* Score, and Percentile Averages at Screening, Baseline, End of Maintenance (EOM), and Annual Growth Rate (Velocity)

Status	Variable	Column 1: Screening			Column 2: Baseline			Column 3: EOM			Column 4: Annual Change (Rate)		
		No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
Total	cm	130	106.63	6.06	134	108.91	6.27	140	114.14	6.67	134	5.63	2.75
M: 104 (74%)	<i>z</i> height	130	0.48	0.93	134	0.45	0.92	140	0.23	0.96	134	-0.22	0.57
F: 36 (26%)	%tile	130	63.41	26.64	134	62.75	26.6	140	56.54	27.94	134	-6.35	17.76
Screening age: 4.40 yr	kg	129	19.15	3.18	133	20.18	3.67	140	21.18	3.80	133	0.87	2.05
Baseline EOM: 337 d	<i>z</i> weight	129	0.77	0.93	133	0.78	0.97	140	0.31	0.95	133	-0.56	0.68
	%tile	129	71.58	25.08	133	71.26	25.74	140	58.98	27.54	133	-14.42	19.57
	BMI	126	16.72	1.63	132	16.91	1.86	140	16.15	1.68	132	-0.991	1.71
	%tile	126	70.97	25.31	132	72.84	25.68	140	59.16	28.98	132	-18.50	31.86
Completers	cm	88	106.70	6.47	91	108.96	6.57	95	115.23	6.64	91	5.41	2.14
M: 72 (76%)	<i>z</i> height	88	0.51	0.98	91	0.46	0.94	95	0.20	0.95	91	-0.26	0.44
F: 23 (24%)	%tile	88	64.05	27.78	91	63.09	27.25	95	55.46	28.40	91	-7.53	13.36
Screening age: 4.4 yr	kg	87	19.19	3.34	92	20.33	3.74	95	21.54	3.81	92	1.07	1.01
Baseline EOM: 401 d	<i>z</i> weight	87	0.78	0.94	92	0.82	0.94	95	0.27	0.92	92	-0.49	0.28
	%tile	87	71.74	24.81	92	72.68	24.47	95	58.08	27.22	92	-13.18	9.68
	BMI	85	16.72	1.61	91	16.97	1.86	95	16.12	1.72	91	-0.765	0.756
	%tile	85	71.94	22.74	91	74.66	23.79	95	58.56	27.62	91	-14.73	16.55
Noncompleters	cm	42	106.48	5.16	43	108.81	5.68	45	111.84	6.20	43	6.10	3.73
M: 32 (71%)	<i>z</i> height	42	0.41	0.83	43	0.43	0.89	45	0.30	1.00	43	-0.12	0.78
F: 13 (29%)	%tile	42	62.06	24.37	43	62.02	25.47	45	58.83	27.11	43	-3.84	24.63
Screening age: 4.4 yr	kg	42	19.08	2.87	41	19.86	3.52	45	20.42	3.71	41	0.43	3.36
Screening-EOM: 202 d	<i>z</i> weight	42	0.75	0.91	41	0.68	1.04	45	0.38	1.01	41	-0.70	1.15
	%tile	42	71.25	25.93	41	68.07	28.43	45	60.89	28.42	41	-17.19	32.23
	BMI	41	16.70	1.70	41	16.78	1.89	45	16.21	1.61	41	-1.49	2.81
	%tile	41	68.98	30.16	41	68.80	29.36	45	60.43	31.96	41	-26.88	51.03

Note: M = male; F = female; BMI = body mass index; d = days.

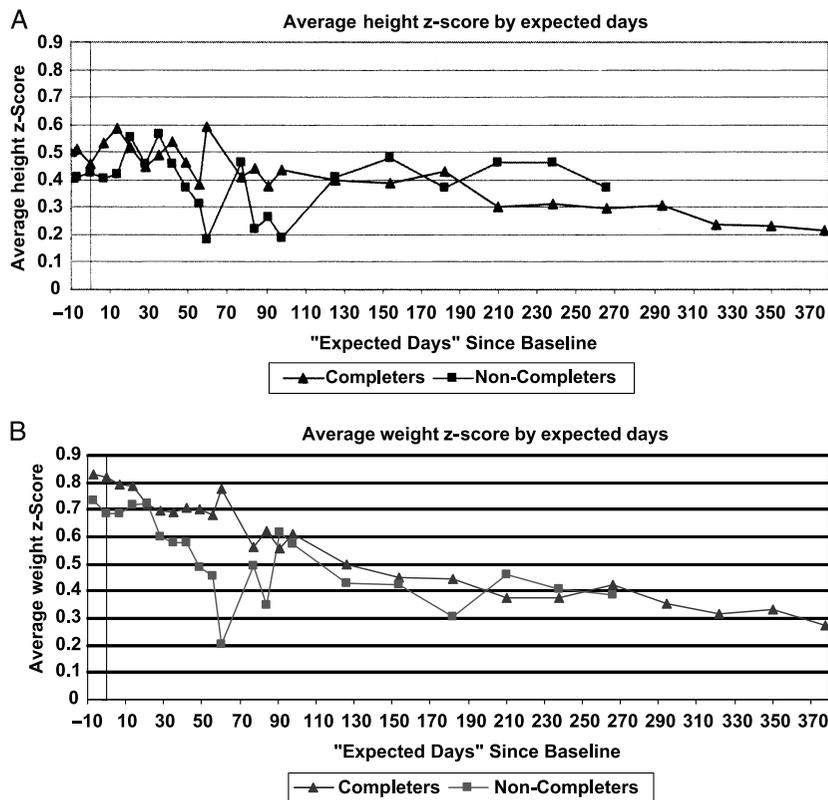
indicating reduction in growth rates for height and weight. Slight differences in the temporal patterns for completers and noncompleters are also suggested by this presentation of group means resulting from a pronounced trough at about 2 months in the lines for noncompleters but not for completers.

The annual growth rates (Table 2, column 4) were smaller than the expected growth velocities (6.79 cm/yr and 2.39 kg/yr) for children this age. This stimulant-related reduction in growth rates was apparent in both subgroups, but the noncompleters, who had a much shorter exposure to medication (an average of 202 days) and a lower total cumulative exposure ( $3,869 \pm 1,956$  mg methylphenidate), manifested nonlinear trajectory over time, so the annual growth rates for the completers are emphasized here. The completers, who were treated for an average of 401 days and had an average cumulative exposure to  $5,770 \pm 2,028$  mg methylphenidate, manifested smaller than expected annual gains in height

( $5.41$  cm/yr  $- 6.79$  cm/yr =  $-1.38$  cm/yr) and weight ( $1.07$  kg/yr  $- 2.39$  kg/yr =  $-1.32$  kg/yr). In relative size measures, reduction in growth rates are shown by an average annual decrease in *z* units for height ( $-0.26$ /yr) and for weight ( $-0.49$ /yr) and in percentile points for height ( $-7.53$ /yr) and weight ( $-13.18$ /yr). Despite this (Table 2, column 3), at the EOM assessment, the average *z* scores were still positive and the percentiles were still  $>50$ , indicating reduced but still larger than expected size. Average body mass index decreased over time, from 16.91 (the 87th percentile) at the baseline assessment to 16.15 (the 71st percentile) at the EOM assessment (Table 2), which was in the direction of normalization.

#### Moderators of Growth Suppression

To search for possible moderators of the stimulant-related reduction of growth velocities, the effects of sex, initial size (*z* height and *z* weight at screening), and initial titration dose were evaluated by entering these variables as



**Fig. 2** Group means across the assessment times (expected number of days from baseline). (A) Height for completers and noncompleters. (B) Weight for completers and noncompleters

covariates in mixed-effects regression analyses. For the total group, only one effect was significant: for *z* weight, initial screening weight was a significant covariate ( $F_{1,137} = 7.89, p < .006$ ), with higher weight at the screening assessment predicting greater change in weight from the baseline to the EOM assessment.

**DISCUSSION**

The analyses of growth data from the PATS reveal two primary findings: (1) before treatment with stimulant medication the group of 140 stimulant-naïve preschool-age children with diagnoses of ADHD was much larger (an average of 2.04 cm taller and 1.78 kg heavier) than expected compared with CDC norms, and (2) after initiation of treatment with stimulant medication, the mean growth rate slowed, and for the children who remain on medication ( $n = 95$ ), this resulted in annual gain that was  $\approx 20\%$  less than expected for height

(5.41 cm/yr – 6.79 cm/yr = –1.38 cm/yr) and  $\approx 55\%$  less than expected for weight (1.07kg/yr – 2.39kg/yr = –1.32kg/yr).

The larger than normal pretreatment size of this sample of preschool-age children with ADHD does not support the logical extension of the hypothesis of maturational lag proposed by Spencer et al. (1996). If this hypothesis, which was developed to account for size differences between ADHD and control in early adolescence, also applies to preschool-age children, then it would predict that the PATS group would be smaller than expected from norms for children 4 to 5 years old. Instead, the observed larger than normal size suggests the opposite pattern (accelerated physical maturation) in this sample of 140 preschool-age children with confirmed diagnoses of ADHD. This discrepancy may be related to the absence in the participants in the PATS of prior treatment with psychotropic medications, which was present in most (89%) of the participants in the study reported by Spencer et al. (1996).

The observed stimulant-related reductions of growth rates for height and weight reported here for preschool-age children are consistent with the observed reductions in school-age participants who were treated with stimulant medication in the 14-month treatment phase of the Multimodal Treatment Study of Children With ADHD (MTA; MTA Cooperative Group, 2004). The PATS and the MTA used similar medication algorithms, with initial double-blind titration and subsequent monthly clinic visits to adjust medication and to monitor adherence, and both may be considered efficacy studies. The MTA and PATS differ from typical effectiveness studies (e.g., Biederman et al., 2003; Klein and Mannuzza, 1988; Kramer et al., 2000; Pliszka et al., 2006; Spencer et al., 1996), which were characterized by some combination of lower doses, less frequent monitoring, prior treatment, lower compliance, noncontinuous treatment, or fewer measures of height and weight. For example, in the chart-review study by Pliszka et al. (2006) in which no growth suppression was detected, the children treated in clinical practice did not take medication on  $\approx 30\%$  of the days during the period when medication was being monitored. The initiation of continuous treatment in stimulant-naïve children in the PATS and MTA protocol may account for differences of the findings from these efficacy studies of stimulant-related growth suppression compared with the findings of some effectiveness studies in the literature, in which prior treatment may have already produced growth suppression or continuous treatment with stimulant medication may have been interrupted by weekend, seasonal, or unscheduled drug holidays or cessation of treatment.

The synaptic mechanism of action of stimulant medication may contribute to the growth suppression effects reported here. Clinical doses of MPH block  $\geq 50\%$  of the dopamine transporter (DAT) in the striatum and produce increased levels of dopamine in that brain region (Neto et al., 2002; Volkow et al., 2002), which is presumed to mediate the efficacy of this treatment. However, stimulant-induced DAT blockade is also expected to increase dopamine levels in other brain regions. For example, in mice lacking a functional DAT, the mutant DAT knockout animals, which would be affected by the equivalent of 100% DAT blockade, show increased hypothalamic dopamine, compared with the wild-type animals. This affects pituitary function and retards growth (Bosse et al.,

1997). Caron (2004) suggested that an initial dopamine deficit may contribute to the greater than expected growth rate and size of stimulant-naïve children with ADHD and that a common synaptic mechanism related to the effects of stimulant medication (DAT blockade and increased synaptic dopamine levels) in different brain regions (hypothalamus and striatum) may mediate this side effect (reduction in growth rate) as well as efficacy (symptom reduction) in stimulant-treated children.

#### Limitations

The PATS protocol did not provide a stimulant-untreated clinical control group. Therefore, comparisons of height and weight before and after treatment were made to population norms. This is a common but serious methodological limitation that has been noted multiple times in the literature (see Joshi, 2002; MTA Cooperative Group, 2004; Spencer et al., 1998). If growth of young preschool-age children with ADHD is accelerated compared with population norms, as suggested by larger than normal size at baseline, then the relative size of a stimulant-untreated control group may have increased over time rather than remain stable compared with population norms. This would operate to increase the degree of stimulant-related reduction in growth rate reported here. Also, the doses used in the PATS were relatively low and homogeneous ( $14.2 \pm 8.1$  mg/day), which may have masked dose-related effects on growth rates.

Another limitation of this report is the short follow-up period described here, which was not sufficient to evaluate the critical issue of long-term effects of the initial growth suppression observed in the first year of treatment with stimulant medication. The long-term effects of the initial stimulant-related growth suppression are uncertain. Two influential reports from follow-up studies have suggested that long-term effects on adult height are negligible (e.g., Klein and Mannuzza, 1988; Kramer et al., 2000), but these reports revealed just average ultimate size (compared with classmate controls or norms) despite larger than average initial size of the participants. Even though not addressed here, the effects of early and prolonged treatment with stimulant medication on ultimate size should be addressed in the naturalistic follow-up of the PATS sample that is in progress.

### Clinical Implications

Based on the findings reported here, families of preschool-age children considering treatment with stimulant medication should be informed that this may result in a reduction in growth rate (velocity) by  $\approx 20\%$  (1.38 cm/yr) for height and  $\approx 55\%$  (1.32 kg/yr) for weight over 1 year of continuous treatment. Consideration of growth-related side effects should be used along with evidence of efficacy in a risk–benefit evaluation of the overall impact of treatment with stimulant medication.

It seems prudent to recommend the assessment of height and weight multiple times each year while a preschool-age child is being treated with stimulant medication to measure growth velocity (Argyle et al., 2003), or the change in relative size over time, rather than just relative size at one point in time. Mei et al. (2004) recommended the use of serial plotting of points on growth charts labeled with lines showing the major percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) and suggested that in clinical practice a change in height or weight that crosses two percentile lines (which they showed rarely occurs in the population of 4- to 5-year-old children) be used as an indication of an aberrant growth trajectory. Recently, the CDC growth charts were expanded to provide *z* scores, which may be more appropriate than percentiles to monitor changes in relative size over time. In clinical practice, three or four assessments of growth per year may be feasible and practical (Pliszka et al., 2006), which may be sufficient for measuring growth rates (velocity) in children treated with stimulant medication.

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**There Is No Meaningful Relationship Between Television Exposure and Symptoms of Attention-Deficit/Hyperactivity Disorder** Tara Stevens, EdD, Miriam Mulsow, PhD

*Objective:* The recent but methodologically limited longitudinal study of the adverse attentional effects of television viewing in early childhood suggests a possible association. The purpose of the present study was to extend this investigation to a more current sample of kindergarten students using structural equation modeling, which allows for the simultaneous evaluation of predictors. *Methods:* Two samples were randomly selected from nationally representative data collected from the Early Childhood Longitudinal Study. A structural equation model was developed positing a relationship between kindergartners' television exposure and subsequent first-grade symptoms of attention-deficit/hyperactivity disorder (ADHD) while controlling for variables related to socioeconomic status and parent involvement. Variables were selected rather than developed and do not include an acceptable measure of ADHD, which limited the scope of the measures used. The model was tested by using the first sample and then cross-validated to the second sample. *Results:* Although the adequate fit of the model to the data suggests that children's television exposure during kindergarten was related to symptoms of ADHD during the first grade, the amount of variance accounted for in the ADHD-symptoms variable revealed television exposure as a weak predictor of later ADHD symptoms. Effect sizes for the relationship between television exposure and symptoms of ADHD were close to zero and not statistically significant. *Conclusions:* Methodologic issues, including participant age, the measurement of ADHD symptoms, and evaluation of the importance of variables, may explain the differences between the present study and the results of others who have found television exposure to be related to attention problems. The measurement of ADHD symptoms through the use of longitudinal databases is an important limitation, because only a small number of items can be selected to represent symptoms. Future research is necessary to address these issues. *Pediatrics* 2006;117:665–672.