

# Growth Deficits in Children With Attention Deficit Hyperactivity Disorder

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**ABSTRACT.** Stimulant-associated growth deficits in children with attention deficit hyperactivity disorder (ADHD) have long been a concern. Height deficits in preadolescence have been reported, but adult heights have been reported to be uncompromised. It is possible that the catch-up growth that occurs is related to ADHD-associated delayed maturation and not to the cessation of stimulant treatment. To date, no consistent neurohormonal pathophysiology to explain stimulant-associated height deficits has been identified nor have the initial associations of height and weight deficits been replicated. Attention deficit hyperactivity disorder is associated with dysregulation of several neurotransmitter systems, especially the catecholamines, that may alter neuroendocrine function and lead to growth delays. The literature on neuroendocrine aspects of growth and treatment in ADHD and on growth in boys with ADHD who are treated with psychotropics is reviewed, and the results of a controlled study in 124 boys with ADHD are presented. Small but significant differences in height were found between children with and without ADHD. However, the height deficits were evident in early, but not late, adolescence and were not related to the use of psychotropic medications. There was no evidence of weight deficits in children with ADHD relative to control subjects and no relationship between measures of malnutrition and short stature was found. These findings suggest that ADHD may be associated with temporary deficits in height gain through midadolescence that may normalize by late adolescence. This effect appears to be mediated by ADHD and not by its treatment. *Pediatrics* 1998;102:501-506; *attention deficit hyperactivity disorder, growth deficit, height deficit, weight deficit, stimulant.*

ABBREVIATIONS. ADHD, attention deficit hyperactivity disorder; GH, growth hormone; IGF-I, insulin-like growth factor I; SDS, standard deviation score(s).

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous disorder of unknown cause. The emerging neuropsychological and neuroimaging literature suggests that abnormalities in frontal networks or frontostriatal dysfunction is the disorder's underlying neural substrate and that catecholamine dysregulation is its underlying pathophysiologic substrate. Recent studies using magnetic resonance imaging of the

brain indicate that there are subtle anomalies in caudate and corpus callosum size and shape or possible reductions in right frontal area in ADHD.<sup>1</sup> These data are consistent with those from a positron emission tomography study that found abnormalities of cerebral metabolism in the prefrontal and premotor areas of the frontal lobe in adults with ADHD who had children with ADHD.<sup>2</sup> Thus, the emerging neuroimaging literature points to abnormalities in frontal networks in ADHD (frontostriatal dysfunction), and it is these networks that control attention and motor intentional behavior.

Data from family-genetic, twin, and adoption studies as well as segregation analysis suggest a genetic origin for some forms of ADHD.<sup>3</sup> However, other causes are also likely, including psychological adversity, perinatal insults and, perhaps, other unknown biologic causes.

The physiologic mechanisms that underlie growth suppression remain obscure, in part because of the rudimentary understanding of the pathophysiology of ADHD. Zametkin and Rapoport postulated "inhibitory influences of frontal cortical activity, predominantly noradrenergic acting on lower (striatal) structures that are driven by . . . dopamine agonists . . ." A theory of adrenergic dysregulation has been proposed, but studies that have investigated urinary, blood, and platelet adrenergic metabolites in children with ADHD and normal children have reported contradictory findings, frequently confounded by recent treatment with stimulants. However, indirect support for this theory of ADHD is derived from the observation that effective medical treatments for ADHD appear to have an adrenergic mechanism of action in common. These medicines include the stimulants, noradrenergic antidepressants (desipramine, bupropion, and monoamine oxidase inhibitors), and  $\alpha$  agonists (clonidine, guanfacine).<sup>5</sup> Other indirect evidence of adrenergic mechanisms in ADHD comes from neuroendocrine challenge studies.

## NEUROENDOCRINE ASPECTS OF GROWTH AND TREATMENT IN ADHD

The potential mechanisms that underlie growth suppression are many, including disorder-specific or medication effects on central nervous system growth factors and hepatic growth factors and direct cartilage effects. Upregulation and downregulation of receptors occur at each level of the growth system,<sup>6</sup> which may explain the short-term effects of medications, possible tolerance to growth inhibition over time, and "catch-up" or compensatory growth after the medication has been discontinued. Weight gain can be suppressed by at least three mechanisms:

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decreased food intake, increased activity, and metabolic shifts (eg, increased fat mobilization). These mechanisms can be related to direct medication effects or to secondary effects such as changes in neuroendocrine hormone secretion.

Although stimulants have potent effects on dopaminergic and noradrenergic systems and these alterations are associated with the hypothalamic-pituitary axis, studies of growth hormone (GH) have not supported alteration of GH by stimulants as a mechanism of stimulant-associated growth suppression. The shared adrenergic mechanism of agents that are effective in ADHD in more than 23 studies appears to be the mechanism that is responsible for the GH response to short-term challenge in normal and psychopathologic populations.<sup>7</sup> Five of six neuroendocrine studies in children with ADHD reported an increased GH response to a short-term stimulant challenge.<sup>8-13</sup> However, it is not clear whether the response to pharmacologic challenge indicates an adequate response from an intact hypothalamic-pituitary neuroendocrine axis or an ADHD-specific pathologic response. Evidence has been mixed on this issue in the few studies with non-ADHD control subjects. Garfinkel and associates<sup>8</sup> and Hunt and colleagues<sup>14</sup> reported significantly greater GH responses to pharmacologic challenge (dextroamphetamine and clonidine, respectively) in children with ADHD than in control subjects without ADHD. However, there were methodologic confounders in both studies: long-term (mean, 8 years) dextroamphetamine treatment in the subjects with ADHD in the study by Garfinkel and associates and the use of unusual control subjects (children with Tourette syndrome and short stature) in the study by Hunt and colleagues. In contrast, Weizman and coworkers<sup>13</sup> reported essentially normal baseline GH levels in children with ADHD, and Greenhill et al<sup>12</sup> reported normal GH responses to insulin-induced hypoglycemic challenge and sleep-related GH secretion. However, Weizman and coworkers compared only baseline, nonchallenge values of GH, and Greenhill et al did not report neuroendocrine data in the control subjects.

Studies of the GH response to pharmacologic challenge in long-term stimulant treatment have also reported mixed results. Aarskog and associates (dextroamphetamine challenge, methylphenidate treatment)<sup>9</sup> and Hunt and colleagues (clonidine challenge, methylphenidate treatment)<sup>14</sup> reported decreased GH responses; Schultz et al (arginine challenge, methylphenidate treatment),<sup>15</sup> Greenhill et al (insulin tolerance test, dextroamphetamine treatment),<sup>12</sup> and Shaywitz et al (methylphenidate challenge, methylphenidate treatment)<sup>16</sup> reported no change in GH responses; and Garfinkel et al (dextroamphetamine challenge, mixed-stimulant treatment)<sup>8</sup> and Weizman et al (methylphenidate challenge, methylphenidate treatment)<sup>13</sup> reported increased GH responses after long-term stimulant treatment.

In addition to the response to provocative stimuli, other measures of GH such as 24-hour or sleep-associated GH secretion may be physiologic parameters that are more germane to growth. Three studies

of long-term stimulant treatment found no abnormalities in the patterns of 24-hour or sleep-associated GH secretion. Two of these studies found no change,<sup>12,15</sup> and one found a small increase<sup>17</sup> in the sleep-associated secretion of GH after  $\geq 1$  year of stimulant treatment.

GH stimulates the production of somatomedin-C (insulin-like growth factor I [IGF-I]) by the liver, which in turn stimulates cartilage growth in bone. There also are direct effects of GH on cartilage, but the IGF-I levels alone are thought to reflect the adequacy of GH production. In fact, it has been postulated that normal levels of IGF-I may rule out GH deficiency.<sup>6</sup> Somatomedin levels were unaffected by long-term treatment in two stimulant studies.<sup>15,18</sup> However, inhibitors of IGF-I action, either endogenous or exogenous (eg, psychotropics) may explain some of the differences in the IGF-I levels measured by radioimmunoassay and those measured by bioassay and, hence, growth deficits. Kilgore and associates<sup>19</sup> found that pemoline, methylphenidate, and methamphetamine all inhibited sulfate uptake by cartilage in vitro, suggesting an interference with cartilage metabolism as a possible mechanism of growth deficits. It is known that malnutrition can lower IGF-I levels despite normal GH levels.<sup>20</sup> The evidence seems to indicate that height suppression is an independent effect, but it is possible that the effects of medications on weight or nutrition could have a secondary effect on any of the systems that regulate height gain.

Psychotropic treatment in children is commonly associated with loss of appetite and weight. Serotonergic mechanisms in the medial hypothalamus are thought to decrease appetite, and noradrenergic mechanisms are thought to stimulate appetite. *d*-fenfluramine, a pure serotonin agonist, tends to cause persistent weight loss.<sup>21</sup> Amphetamines may cause anorexia by a different mechanism, that of dopamine agonist action in the lateral hypothalamus, typically with rapid tolerance developing.<sup>22</sup>

#### GROWTH AND THE TREATMENT OF ADHD

There have been long-standing concerns about growth deficits in children with ADHD. Studies that have reported suppressed height gains have suggested that there is a causal relationship between the therapeutic agent and height deficits. Fifteen of 25 medium-term studies of growth in children with ADHD who were treated with stimulants reported initial suppression of height gain. Nine of 18 methylphenidate studies found initial height deficits,<sup>23-31</sup> and 9 did not.<sup>17,32-39</sup> Four of 5 dextroamphetamine studies found initial height gain deficits,<sup>12,23,26,27,40,41</sup> and 1 did not.<sup>35</sup> Two studies of pemoline reported initial height gain deficits.<sup>18,42</sup> However, complex methodologic issues have confounded direct comparisons between these two studies. These methodologic issues include different methods of assessing growth, the use of control subjects (either normal subjects or untreated children with ADHD), insufficient durations to investigate potential tolerance, and the use of different age groups (prepubertal, pubertal) to investigate developmental issues.

Previous studies of growth in ADHD have used more than eight different methods of assessing growth, including direct comparisons of mean heights and frequency percentiles from standardized growth charts,<sup>31</sup> methods that are subject to artifactual distortion and low sensitivity.<sup>43</sup> Sensitivity is an important issue in evaluating growth deficits, because the mean height deficits generally have been small. Although the use of standard deviation score(s) (SDS) to assess height deficits is universally accepted as the most valid method for assessing height variations in pediatric subjects,<sup>43</sup> it has rarely been used in studies of growth deficits in children with ADHD.<sup>31</sup>

#### THE MASSACHUSETTS GENERAL HOSPITAL STUDY OF GROWTH IN ADHD

In a recent study, we found modest height deficits in 124 referred boys with ADHD relative to 109 control subjects.<sup>44</sup> However, these height deficits were evident only in early adolescence and were not related to weight deficits or stimulant treatment. Of the 124 boys, 110 (89%) had been treated with pharmacologic agents at some time, 87 (70%) of the 124 within the past 2 years. In the preceding 2 years, 56 (45%) of these 124 boys had been treated with an average dose of methylphenidate (or its equivalent) of  $38 \pm 24$  mg/d and, of these, 40 (71%) had been treated continuously.

The magnitude of the mean height deficits (2.1 cm, age-corrected) found in our study was consistent with the 1- to 3-cm height deficits in previous reports. For example, Safer and colleagues<sup>23,26,27</sup> reported a suppression of gain in height of 3 cm over 3 years. Mattes and Gittelman<sup>25</sup> reported a 3.3-cm deficit in expected height gain over a 4-year follow-up. Similarly, Spencer and associates<sup>31</sup> reported modest (1.5-cm) treatment-associated deficits in height gain in children with ADHD who were treated for >1 year with relatively high doses (1 mg/kg/d) of methylphenidate.

There was no evidence of stimulant-associated suppression of weight gain in the children with ADHD in our study. In fact, using a measure of malnutrition (weight as percentage of expected [or standard] weight for height),<sup>31,45</sup> we found evidence of more than adequate body mass in our sample. Our results are consistent with some, but not all, of the rather mixed and contradictory results in the literature, with some studies reporting modest mean weight deficits<sup>17,24–26,28,31,33</sup> and others reporting none.<sup>30,34–38</sup> Overall, it appears that treating ADHD with stimulants may result in small effects in weight gain in some children that usually can be offset by adjusting the timing of the medication and by food supplementation.

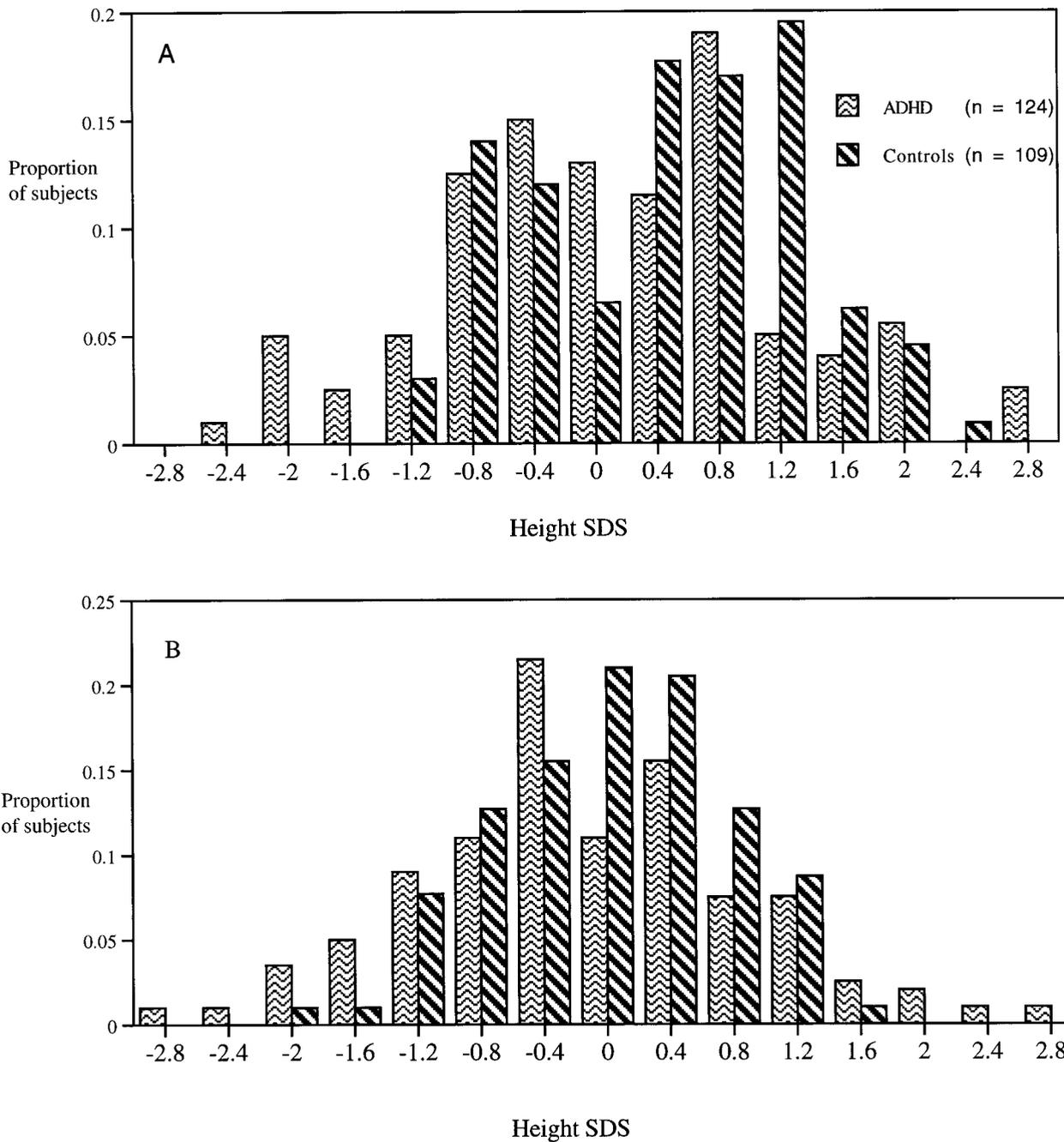
In addition to the finding of no suppression of weight gain in our study, there also was no association between weight loss and height deficits. The first reports linked stimulant-associated weight loss with suppression of height gain,<sup>26</sup> but the consensus in more recent reports has been that weight and height suppression is independent in children with ADHD who are treated with stimulants.<sup>18,23,24,30,31</sup>

The mean height deficits among children with ADHD are small; however, a subgroup of children with ADHD does have clinically worrisome height suppression. We examined extremes of stature by arbitrarily defining a cutoff of more than 2 SDs (eg, ~14 cm in 15-year-old boys) below the average height of the non-ADHD control subjects. Using this criterion, we found that 10% of the children with ADHD (but only 1% of the control subjects) were very short (Fig 1). This finding indicates that a small minority of children with ADHD may have marked delays in height gain. Because it is not known whether this subgroup of children will outgrow these deficits, it is very important that they be observed closely and that their growth be monitored closely while they are being treated with psychotropic agents.

The heights of the children in our study were converted to SDS by using National Center for Health Statistics growth tables.<sup>46</sup> The difference in height SDS between the children with ADHD and the control subjects was statistically significant (0.21 vs 0.47;  $P = .03$ ), but the mean height SDS were >0 in both groups, indicating that they were slightly taller than the population norms. This is consistent with a cohort effect in which each generation tends to be taller than its predecessor.<sup>47</sup> Thus, studies of growth in ADHD that use population norms for comparisons are unlikely to detect the modest magnitude of the mean differences in heights because of this cohort effect.

Height deficits in our study were evident in younger, but not older, children and were not affected by recent (within the past 2 years) robust treatment with stimulants (Fig 2). Similar developmental variations in height deficits have been reported by other investigators; however, they often have been ascribed to the termination of treatment. Hechtman et al<sup>48</sup> and Gittelman and coworkers<sup>49</sup> reported that the final mean height in adults who had had ADHD as children was comparable with that in control subjects despite preadolescent height deficits in the former. Gross was unable to find height deficits in adolescents despite earlier decreases in their height percentiles and continued treatment.<sup>35</sup> These reports, along with our findings on the lack of a treatment effect, suggest that these height deficits are not permanent, but may be the result of disorder-specific developmental delays in the tempo of height gain.

To differentiate disorder from treatment-related growth effects, studies must compare treated children with ADHD with untreated children, and not with unaffected control subjects. Three of the six previous studies that used untreated children with ADHD for comparisons reported stimulant-associated height deficits in children with ADHD<sup>26,27,50</sup> and three did not.<sup>33,36,38</sup> However, these studies assessed preadolescent subjects and could not fully assess any possible normalization of height with later development. Three of four studies that evaluated the impact of drug holidays in children with ADHD found that continued stimulant treatment was associated with height suppression and that rebound growth oc-



**Fig 1.** Age-corrected (A) and parent- and age-corrected (B) height SDS in ADHD and control probands. Age-corrected height: height values were converted to a height SDS defined as the difference in the height of a subject from the mean height of normal boys of the same age divided by the SD for height for that subgroup. Parent- and age-corrected height: the relationship between a child's height and the parents' heights was examined with regression analysis in control subjects. The estimated regression equation was used to determine the child's predicted height from the parents' heights. The difference between the child's actual height SDS and the predicted height based on the parents' heights was defined as the parent- and age-corrected height.

curred during drug holidays.<sup>23,24,27,30</sup> However, these effects could be spontaneous normalization of height gain over time; other studies have shown catch-up gains in height during treatment in children with ADHD.<sup>18,24,35</sup> Our findings are consistent with some, but not all, of the previous findings, and they suggest that the stimulant-associated height deficits reported previously in ADHD might be temporary and early manifestations of ADHD itself and not complications of its treatment.

The apparent slower tempo of height gain in our

sample was not associated with evidence of delayed pubertal development. For assessing pubertal stages, the children completed a self-report questionnaire in which they were asked about the presence or absence of a full beard, axillary hair, and pubertal hair as well as the age at attainment of each stage. On the basis of these questions, estimates of Tanner stages were developed as follows: attainment of pubertal hair, Tanner stage 2 or 3; attainment of axillary hair, Tanner stage 3 or 4; and attainment of facial hair, Tanner stage 4 or 5. The ages at the onset of the Tanner

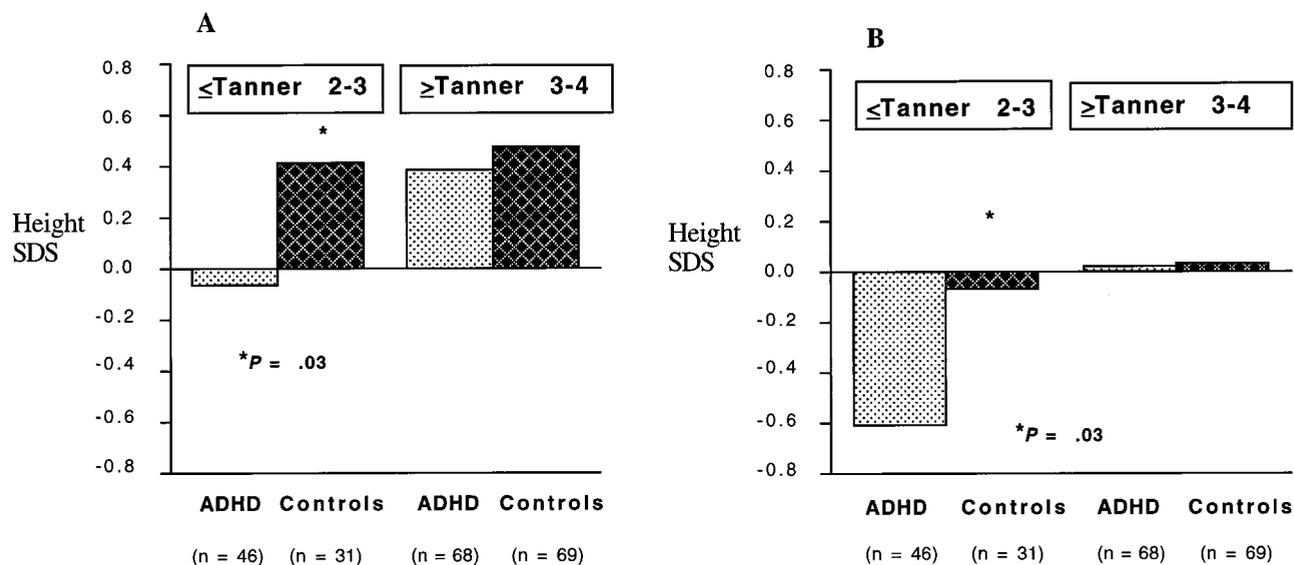


Fig 2. Age-corrected (A) and parent- and age-corrected (B) height SDS in probands by estimated Tanner stage. Adapted from Spencer et al.<sup>44</sup>

stages were equivalent in the children with ADHD and the control children, and were consistent with the published ages at the onset of the Tanner stages in the general population (12 years for initial pubic hair, ~13.5 years for axillary hair, and ~14.5 years for beard).<sup>51,52</sup> A similar dissociation between the Tanner stages and the timing of the pubertal height gain has been reported in boys in the general population.<sup>51</sup> The reasons for the dissociation observed between height gain and pubertal development remain unknown and require additional study, and our findings suggest that height delays in ADHD are not accounted for by pubertal delays.

Our findings may provide important clues about growth in ADHD, but it should be noted that our study examined growth parameters in younger and older children with ADHD at only a single point in time. Inferences about development in this study should be evaluated in future longitudinal studies.

### CONCLUSIONS

The underlying pathophysiology of ADHD remains unknown. A theory of adrenergic dysregulation has been proposed that would account for the common adrenergic mechanism of action of effective treatments for ADHD as well as findings from neuroendocrine challenge studies. However, the effects of stimulants on GH and appetite regulation may be incidental effects on structures that are not related to the pathophysiology of ADHD.

Our findings confirm previous reports of small but statistically significant deficits in height gain in children with ADHD. In addition, our findings show that these height deficits may normalize in late adolescence regardless of whether medication is used. These findings are consistent with the hypothesis that ADHD may be associated with a temporary delay in the tempo of gain in height. If confirmed, these findings can be reassuring to patients and their

families, and could provide new leads to the pathophysiology of ADHD.

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## **Growth Deficits in Children With Attention Deficit Hyperactivity Disorder**

Thomas Spencer, Joseph Biederman and Timothy Wilens

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