Stimulant medication effects on growth and bone age in children with attention-deficit/hyperactivity disorder: a prospective cohort study
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Stimulant medication is known to cause transient weight loss and slowing down of growth, but whether it delays physical maturation is unclear. We studied growth and bone age over the first 3 years of treatment in children with attention-deficit/hyperactivity disorder (patients) compared with healthy siblings (controls). Bone age was estimated blindly by two independent radiologists using Tanner and Whitehouse version 3. Dexamphetamine or methylphenidate was titrated and continued when clinically indicated. Forty out of 73 patients, together with 22 controls, completed the study. There were no significant growth differences between the two groups at baseline. Despite slower growth on treatment (5.1 cm/year, 95% confidence interval (CI): 4.7–5.5, vs. 6.3 cm/year, 95% CI: 5.7–6.8, \( P = 0.002 \); and 2.7 kg/year, 95% CI: 2.1–3.3, vs. 4.4 kg/year, 95% CI: 3.5–5.3, \( P = 0.005 \)), the patients showed no significant maturational delay (RUS score: 49 U/year, 95% CI: 44–55, vs. 55 U/year, 95% CI: 47–63, \( P = 0.27 \)). A subgroup of patients underwent serial biochemistry and dual-energy X-ray absorptiometry, recording a significant reduction in fat (5.61 ± 3.56–4.22 ± 3.09 kg, \( P < 0.001 \)) and leptin (3.88 ± 2.87–2.57 ± 1.94 ng/ml, \( P = 0.017 \)). The pattern of change in height z-score over time was modified by the dose of medication \( ( P \) for interaction = 0.024). We found no medication effect on the rate of maturation, which was instead predicted by baseline leptin \( ( P = 0.035 \) controlling for age and sex). *Int Clin Psychiatr Pharmacol* 00:000–000

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**Introduction**

Children treated for attention-deficit/hyperactivity disorder (ADHD) may initially experience slower growth rates, which normalize over 3 years (Safer and Allen, 1973; Poulton and Cowell, 2003; Poulton, 2005; Farone et al., 2005; Charach et al., 2006; Swanson et al., 2006; Swanson et al., 2007). Whether this is solely attributable to stimulant treatment has been a debated topic, the alternative view being that slower growth results from associated delays in cognitive and physical maturation (Oettinger et al., 1977; Hanc and Gieslik, 2008; Gustafsson et al., 2010). This latter position has gained further credence from data showing delayed maturation of the cerebral cortex in ADHD patients (Shaw et al., 2007).

The rate of physical maturation on stimulant medication is important because, if children are growing more slowly but continuing to mature at the normal rate, their epiphyses could fuse before they reach their full growth potential. Several cross-sectional studies looking at bone age have found no delay (Oettinger et al., 1977; Schlager et al., 1979; McGee et al., 1985), but their sensitivity could be limited by the wide range of normality. We could find no longitudinal studies investigating the rate of bone age progression with growth in children with ADHD.

Our aims were to compare the growth parameters and bone age of children with ADHD starting stimulant treatment with those of their untreated, normal siblings at baseline and over the subsequent 3 years. Our hypotheses were that, before treatment, ADHD itself would not be associated with any significant differences in growth parameters or bone age but that on stimulant medication bone age would be delayed proportionately with growth in height.

**Patients and methods**

This was a prospective cohort study carried out in a paediatric private practice in western Sydney, Australia, with 3 years’ follow-up. Ethical approval was granted by our institution’s Human Research Ethics Committee (02/013).

**Participants**

The children with ADHD were referred for behavioural concerns and were aged less than 12 years. ADHD was diagnosed according to the criteria of the American Psychiatric Association (DSM-IV) and included a detailed interview and physical examination by an experienced paediatrician (A.S.P.). Checklists of DSM-IV criteria for ADHD (and for oppositional defiant disorder when...
symptoms were suggestive) were completed by parents and teachers. All were stimulant naive and otherwise healthy and had received appropriate nonmedical intervention. Available healthy siblings aged less than 12 years were recruited as controls. Written informed consent was given by the parents, and all children assented.

The first 30 children with ADHD aged less than 9 years whose parents consented also underwent dual-energy X-ray absorptiometry and fasting blood tests (Poulton et al., 2012), including insulin, ghrelin (promotes appetite) and leptin (suppresses appetite and correlates with fat mass; Saad et al., 1998).

Medication protocol
Initial dose titration used immediate release formulations aiming for maximum improvement at the lowest possible dose. Once stabilized, reviews were at least 6 monthly, with medication adjusted using information from the parents and IOWA Conners Rating Scales completed by the teacher (Pelham et al., 1989). Side effects were established through direct questioning, and medication consistency was graded: 4 – same dose every day; 3 – medication every school day plus some on some non-school days; 2 – medication on school days only; 1 – medication less often than every school day.

Measurements
Children were weighed and measured in light clothing to the nearest 1 mm and 0.1 kg using a wall-mounted stadiometer and electronic scales. Age and sex-corrected z-scores were calculated using CDC reference data (Cole, 1990; Kuczynski et al., 2000). (The z-score standardizes the child’s measurement by age and sex; it equates to the number of SDs the measurement is above or below the reference mean.)

Radiographs of the nondominant wrist and hand were taken at baseline and 3 years and read independently by two radiologists blinded to date, age and group allocation. Bone age was calculated using the method of Tanner and Whitehouse, which stages the radius, ulna and 11 small bones of the hand to compile an RUS score that is converted to bone age using sex-specific reference data (Tanner et al., 2001). We used Tanner and Whitehouse version 3, an update made in 2001, to reflect the secular trend towards earlier maturation (Ahmed and Warner, 2007). We could find no relevant data for calculating the sample size required for comparing longitudinal changes in bone age.

Data analysis
The mean of the two radiologists’ scores was used for analysis. Within-subject comparisons used paired t-tests. Comparisons between groups used two-sample t-tests; participants were not yoked to their siblings for analysis. This is because they were not matched with their siblings for age and sex. Comparisons used measures that were already corrected for sex (bone age, z-scores for growth data) or used linear modelling adjusting for sex and age as appropriate. Categorical comparisons were made used the \( \chi^2 \)-test. Correlations were determined using the Pearson correlation test. Repeated-measures data were analysed using a linear model (GEE). For change in height, the interaction between change in RUS and group was calculated, adjusting relevant covariates. All analyses were two-tailed, and statistical significance was taken as \( P \) value less than 0.05.

Results
Sample
From July 2003 to December 2009, 143 eligible children with ADHD were seen, diagnosed and treated (Fig. 1). Parents of 112 children consented, and 73 children aged 7.96 ± 1.82 years (range: 4.08–11.61 years) with ADHD and 35 siblings aged 7.65 ± 2.45 years (range: 2.50–11.32 years) \( (P = 0.50) \) presented to Nepean Hospital for baseline radiographs. Radiographs were repeated after 3 years in 40 patients (all still on treatment) and 22 controls aged 10.96 ± 1.59 and 10.56 ± 2.69 years, respectively \( (P = 0.52) \).

Boys outnumbered girls in the ADHD group but not in the control group (59/73 and 14/35, respectively, at baseline; \( \chi^2 = 19, P < 0.001; \) and 32/40 and 9/22, respectively, at 3 years; \( \chi^2 = 9.7, P = 0.002)\). The children with ADHD who were not recruited were not significantly different from the included children in terms of baseline age (7.79 ± 1.77 years, \( P = 0.55) \) or sex ratio (76% boys). The 33 children with ADHD who did not have second radiographs (including one whose radiograph was lost) were comparable to the completers in age (8.12 ± 2.20, \( P = 0.52) \), sex ratio (82% boys) and baseline symptom score on the IOWA Conners Rating Scale (16.8 ± 7.1 and 15.3 ± 7.7, respectively, \( P = 0.47) \). After 3 years, 14 children without second radiographs were still on treatment and 10 were known to have ceased medication. Two-year growth velocities on treatment were available in 16 children without second radiographs and were not significantly different from the completers (height velocity: 5.1 ± 1.3 vs. 5.0 ± 1.1 cm/year, \( P = 0.61) \), and 2.1 ± 2.4 vs. 2.3 ± 1.7 kg/year, \( P = 0.83) \) respectively).

The majority of children with ADHD had combined type (80%); Oppositional defiant disorder was diagnosed in 30 (41%).

Dose of medication
After 1 year, 85% of patients were on methylphenidate (mean: 25.5 ± 8.7 mg/day; 0.87 ± 0.34 mg/kg/day) and 15% on dexamphetamine (mean: 10.4 ± 4.8 mg/day; 0.30 ± 0.15 mg/kg/day), with 31% taking the same dose every day and 58% taking medication on school days but less often or not at all on non-school days. After 3 years, 93% were on methylphenidate (mean: 35.2 ± 16.3 mg/day; 1.00 ± 0.45 mg/kg/day) and 7% on dexamphetamine (mean: 10.0 ± 2.5 mg/day; 0.34 ± 0.08 mg/kg/day); 42% took the same dose every day.
and 51% took medication on school days but less often or not at all on nonschool days. The main reason for changing from dexamphetamine to methylphenidate was the availability of subsidized sustained release formulations for methylphenidate, which were taken by 34% at 1 year and by 72% at 3 years. After 3 years, intermittent treatment correlated with age, with younger children taking medication more consistently (r = −0.34, P = 0.02), but there was no significant correlation between dose in mg/kg and age (r = −0.10, P = 0.52) or weight (r = −0.25, P = 0.10). Intermittent dosing correlated with daily dose in mg/kg, such that children on higher doses took medication more consistently (r = 0.59, P < 0.001).

**Side effects**

Side effects were reported in 80%, mainly during the first 2 months. These were mainly mild but 18% required a dose reduction and 11% changed medication. Three children were changed from dexamphetamine to methylphenidate and four children were trialled on atomoxetine. Two ceased medication completely because of side effects: one developed obsessional behaviour and the other experienced appetite suppression, insomnia, headache and tics. The most prevalent side effects were gastrointestinal symptoms (53%, including 39% with stated appetite suppression) and insomnia (47%). Melatonin was prescribed for insomnia for 13 children. The children with gastrointestinal symptoms lost an average of 0.82 ± 0.89 kg in the first 2 months, which was not significantly different from the 0.52 ± 0.87 kg lost by those who reported no gastrointestinal symptoms (P = 0.16).

**Height and weight**

There were no significant differences at baseline between groups in terms of age-corrected and sex-corrected height, weight and BMI (Table 1). After 3 years on treatment the children with ADHD weighed significantly less than did controls after correction for age and sex. There were no other significant differences in cross-sectional growth data between groups.

Over 3 years the patients gained significantly less height and weight compared with the sibling controls (Table 1 and Figs 2 and 3), with weight loss in the first 6 months (0.6 ± 2.2 kg, P = 0.046). The correlations between the changes from baseline in height and weight z-scores in the ADHD patients progressively increased during the first 2 years (Table 2). Higher baseline weight was associated with more weight loss (r = −0.47, P < 0.001, n = 58, and r = −0.26, P = 0.036, n = 64, after 1 and 6 months, respectively).

The dose taken at 1 year was used for analysis of medication effects. Younger baseline age and higher medication dose (mg/kg) were independent predictors of the reduction in height z-score at 3 years (P < 0.001 for each) but intermittent dosing and use of sustained release formulations were not. Analysis using repeated measures
showed that the pattern of change in height and weight $z$-scores over time was modified by baseline age ($P$ for interaction = 0.011 and 0.028, respectively), with younger children showing greater reductions in $z$-scores. The medication dose also modified the pattern of change over time in height $z$-score ($P$ for interaction for dose in mg/kg/day = 0.024) and weight $z$-score ($P$ for interaction for dose in mg/kg/day = 0.0008 and in mg/kg/day = 0.007), with larger doses having a greater effect. There was a significant effect of intermittent treatment at 12 months on change in weight $z$-score ($P$ = 0.011) but with no significant time interaction. Among the patients who had biochemical data, it was seen that baseline ferritin modified the pattern of change in height $z$-score over time ($P$ for interaction = 0.032, $n$ = 20).

The children with oppositional defiant disorder were on higher doses/kg ($P < 0.01$), took medication more consistently ($P < 0.01$) and grew more slowly in height and weight during the first year ($P < 0.05$).
Table 2  Correlations between changes in height and weight z-scores from baseline for different time periods for the children with attention-deficit/hyperactivity disorder on treatment and their sibling controls

<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>$\Delta$h</th>
<th>$\Delta$w</th>
<th>Correlation (Pearson’s $r$)</th>
<th>Paired $t$ test* ($P$)</th>
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<tr>
<td>ADHD patients</td>
<td></td>
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<td>6 months</td>
<td>64</td>
<td>$-0.12$ ($-0.16$–$0.08$)</td>
<td>$-0.43$ ($-0.50$–$0.36$)</td>
<td>0.16, $P=0.19$</td>
<td>$&lt;0.001$</td>
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<tr>
<td>1 year</td>
<td>64</td>
<td>$-0.22$ ($-0.27$–$0.16$)**</td>
<td>$-0.50$ ($-0.59$–$0.42$)**</td>
<td>0.28, $P=0.02$</td>
<td>$&lt;0.001$</td>
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<tr>
<td>2 years</td>
<td>55</td>
<td>$-0.31$ ($-0.39$–$0.22$)**</td>
<td>$-0.55$ ($-0.66$–$0.44$)**</td>
<td>0.61, $P&lt;0.001$</td>
<td>$&lt;0.001$</td>
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<tr>
<td>3 years</td>
<td>47</td>
<td>$-0.33$ ($-0.44$–$0.23$)**</td>
<td>$-0.60$ ($-0.73$–$0.48$)**</td>
<td>0.49, $P=0.001$</td>
<td>$&lt;0.001$</td>
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<td>Sibling controls</td>
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<tr>
<td>1 year</td>
<td>20</td>
<td>$-0.01$ ($-0.11$–$0.09$)</td>
<td>$0.06$ ($-0.09$–$0.21$)</td>
<td>0.47, $P=0.04$</td>
<td>0.21</td>
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<tr>
<td>2 years</td>
<td>14</td>
<td>$-0.05$ ($-0.21$–$0.11$)</td>
<td>$-0.15$ ($-0.36$–$0.07$)</td>
<td>$-0.13$, $P=0.85$</td>
<td>0.42</td>
</tr>
<tr>
<td>3 years</td>
<td>19</td>
<td>$-0.04$ ($-0.20$–$0.12$)</td>
<td>$-0.07$ ($-0.28$–$0.14$)</td>
<td>0.11, $P=0.66$</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Mean (95% confidence interval) are shown. Controls were not weighed and measured at 6 months. ADHD, attention-deficit/hyperactivity disorder. *Within-subject comparisons of changes in height and weight z-scores. **$P<0.01$; ***$P<0.001$ compared with controls (two-sample $t$ test).

Bone and RUS score

The correlation between the reporting of the radiologists was $r=0.96$ ($P<0.001$). There was a significant correlation between the change in bone age and change in RUS score ($r=0.62$, $P<0.001$) but no significant differences between groups at baseline or after 3 years in either measure (Table 1).

After controlling for age and sex, baseline weight was a significant independent predictor of the rate of change of RUS score ($P=0.021$), but baseline height and group allocation (ADHD patients or sibling controls) were not ($P=0.32$ and 0.45, respectively). Among patients with biochemical data, baseline leptin was a significant predictor of the rate of change of RUS score ($P=0.035$) after controlling for age and sex. A significant reduction in leptin in the first 3 months ($−1.31±2.17$ ng/ml, $P=0.017$, $n=19$) correlated with the rate of change in RUS score ($r=−0.76$, $P=0.004$, $n=12$), but this was no longer significant after controlling for baseline leptin. The change in vitamin D correlated with the change in leptin ($r=0.61$, $P=0.012$) but did not predict the rate of change in RUS score.

Baseline leptin was significantly related to fat mass ($r=0.76$, $P<0.001$, $n=21$) and the changes in leptin and fat mass in the first 3–6 months also correlated ($r=0.64$, $P=0.008$, $n=16$). The significant reduction in fat ($−1.30±0.89$ kg, $P<0.001$, $n=20$) correlated with the rate of change in RUS score ($r=0.75$, $P=0.003$), but this was not significant after controlling for baseline fat. Measures of lean tissue, bone mineral content and bone mineral density, medication (dexamphetamine or methylphenidate) and medication dose were not significant predictors of the rate of change of RUS score after controlling for age and sex. None of the above analyses were significant for the rate of change in bone age.

Relationship between change in height and change in RUS score

For the change in height, the interaction between change in RUS score and group was $P=0.001$, adjusting for sex and time interval. As the timing of the height and weight measurements did not always coincide with the radiographs, we repeated this calculation by incorporating a correction for height when there was a discrepancy in timing of more than 2 weeks (35% of measurements). This was done by converting the growth data to age-corrected and sex-corrected z-scores, and the z-score was used to calculate the corrected height at the time the radiograph was taken. For the change in height (corrected), the interaction between change in RUS and group was $P=0.015$, adjusting for sex and time interval.

The major outcomes were not predicted by baseline levels or changes in fasting insulin, glucose, albumin, prealbumin, transferrin, insulin-like growth factor 1, insulin-like growth factor binding protein 3 or ghrelin.

Discussion

Medical treatment for ADHD provides a unique opportunity to investigate the immediate and longer-term effects of a sustained change in energy balance on growing children. In untreated ADHD our hypothesis was supported as we found no delays in growth or bone age. However, slower growth on treatment did not correspond to any delay in bone age. Instead, linear modelling indicated that ADHD children were maturing more quickly than would be expected for their growth in height. The pattern of change in height z-score with time was modified by the dose of medication but the change in RUS score was predicted by baseline energy stores.

Limitations include the small sample sizes and the relatively short period of follow-up (3 years). The attrition due to ceasing medication was anticipated (Bussing et al., 2005), but not the attrition related to the inconvenience of attending hospital for the radiographs. Arguably, siblings may not be the best choice for healthy controls as they may share a genetic predisposition to ADHD, with pairs of brothers often both affected, contributing to the sex disparity between groups. However, siblings might control for any familial growth pattern unrelated to ADHD, and ethical considerations limited controls to siblings of...
index cases. The sex disparity was controlled for statistically.

The main strengths are the longitudinal data for growth and bone age in stimulant-naive children and the independent scoring by two radiologists. Analysis using the raw RUS scores allowed associations to be detected that were not apparent after conversion to bone age, which involved introducing an additional source of variability, reducing the sensitivity of the measure.

We suggest that the attenuated height velocity is secondary to changes in energy balance due to stimulant-related appetite suppression. The effect on growth was dose related, with greater attenuation of height and weight observed in children with oppositional defiant disorder, who took medication more consistently and at higher dose. The decline in weight z-score occurring more rapidly but correlating significantly with the decline in height z-score would be consistent with the notion that a negative energy balance induced a slower height velocity. However, indicators of changes in energy balance, such as the initial changes in glucose, leptin and fat mass, had no predictive value for the changes in height z-score. This may be because they were not representative of the changing energy balance over the longer time period. The consistency of the stimulant effect on growth suggests change in a regulated process. Although reduced appetite was not invariably reported, weight loss occurred despite parents’ efforts in encouraging their children to eat, which may suggest that the stimulant interferes with appetite control. We found no evidence that the effect on appetite was mediated by changes in leptin, ghrelin or insulin (Poulton et al., 2012). On the contrary, the reduction in leptin associated with loss of fat may have helped to limit the extent of weight loss.

Our finding of no significant delay in bone age in ADHD is similar to the findings from three cross-sectional cohort studies (Schlager et al., 1979; McGee et al., 1985; Gustafsson et al., 2008). Our data did not support the suggestion that children with ADHD who are less psychologically mature at baseline, as determined by their baseline IOWA Conners ratings, show more rapid bone age maturation (Gustafsson et al., 2010), although of course we had only 3 years of follow-up.

Although the significant inverse correlation between the change in leptin in the first 3 months and the change in RUS score over 3 years might suggest that a discrete period of fat loss in childhood could be a stimulus to more rapid physical development, we suggest that greater fat losses simply identified children with higher baseline fat who were already likely to mature more rapidly. This is consistent with other studies that have shown that fatter children lose more weight on stimulant medication (Schertz et al., 1996; Faraone et al., 2005).

Our finding of normal bone age progression despite slower growth contradicts our expectation that physical maturity would be closely related to stature. However, nutritional status can modify the relationship between growth and physical maturation. Reference data for bone age assume ‘normal’ nutrition, and the data of Tanner and Whitehouse have been revised because of nutritional increases driving earlier maturation (Ahmed and Warner, 2007). Conversely, growth delays from chronic undernutrition may be associated with even more delayed maturation, with undernourished girls actually being taller at menarche than well-nourished girls (Dreizen et al., 1967). Our study children with ADHD had a discrete event – starting stimulant medication – which initiated a change in their nutritional status and impacted on growth. The weight z-scores declined more rapidly than did height z-scores; it is possible that the rate of physical maturation might also have been declining but over a longer time frame. This notion is supported by data on pubertal development in boys with ADHD (Poulton et al., 2013). These boys, who had been on stimulant medication for an average of 6 years, showed no maturational delay in early puberty compared with community controls, but there was evidence that they progressed more slowly through puberty, with a later growth spurt. Another recent study has shown a delay in the pubertal growth spurt that correlated with the duration of stimulant treatment (Harstad et al., 2014). These findings are consistent with a deceleration in the rate of physical maturation during puberty and later catch-up growth.

Our finding of indicators of baseline nutritional status to be the most reliable predictors of the rate of bone age progression over the first 3 years of stimulant treatment does not exclude the possibility of subsequent attenuation of physical maturation in children treated for a longer period of time. This could be further investigated by comparing the relationships between growth, bone age and stage of puberty in adolescents on long-term treatment for ADHD with those of healthy controls.

**Conclusion**

Children with untreated ADHD showed normal growth parameters and bone age, but they had growth delay with a normal rate of maturation on treatment. The growth delay was medication dose related but the rate of maturation was determined by baseline characteristics. Although this lack of concordance between growth and maturation could have adverse implications for growth potential, an alternative possibility is that the usual correlation between growth in height and bone age does not hold for children treated with stimulant medication.

Treatment-related growth attenuation is likely to increase the prevalence of short stature in children with ADHD. If these children undergo bone age assessment, it should be kept in mind that within the first 3 years of
treatment bone age is unlikely to be delayed. This may increase the inaccuracy of using bone age in the estimation of adult stature (Roche et al., 1975).

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Conflicts of interest
A.S.P. has shares in GSK, has served on the Advisory Board and received conference support from Shire. For the remaining authors there are no conflicts of interest.

References