Dear Editor,

Cushing’s syndrome (CS) is a rare disease in children it is associated with weight gain and stunting of their linear growth (McArthur et al. 1980, Magiakou et al. 1994a, Stratakis 2012). In this study, we assessed growth in pediatric patients with CS after cure, caused by either adrenocorticotropic hormone (ACTH)-dependent Cushing’s disease (CD) or a form of ACTH-independent CS, and patients with micronodular adrenal hyperplasia (MAH).

We reviewed medical records of patients who had successful transsphenoidal surgery or adrenalectomy at the NIH between the years of 2002 and 2012. A total of 18 children with CD (9 F, mean age 12.2±3.0 years) and 19 children with MAH (15 F, mean age 9.8±4.4 years) were included. All patients were evaluated under the clinical protocol 97CH0076 and 95CH0059 that were approved by the NICHD Institutional Review Board. Informed consent was signed from the patients’ parents. The diagnosis of CS was established as previously reported (Batista et al. 2007). Patients that were at Tanner stage 5 at the time of surgery were excluded from the analysis of annual growth velocity and insulin-like growth factor 1 (IGF1) z scores.

The mean follow-up after surgery was 402±27 days for the CD and 365±87 days for the MAH patients (P=0.09). No significant difference was found in terms of mean age (although CD patients were 2.4 years older), gender distribution, duration of symptoms, midnight cortisol levels, IGF1 z score, and mean urinary free cortisol at the time of surgery. The demographics are presented in Table 1. The baseline height (Ht) z scores and BMI z scores were not significantly different between the two groups (P=0.85 and P=0.66 respectively; Fig. 1A).

The mean Ht z score in CD before and after surgery was −1.24±1.14 and −0.91±1.30 respectively (P=0.03). The mean Ht z score in MAH before and after surgery was −1.33±1.64 and −0.62±1.37 respectively (P=0.0002; Fig. 1B). The mean BMI z score in CD before and after surgery was 2.07±0.62 and 1.13±1.03 respectively (P<0.0001). The mean BMI z score in MAH before and after surgery was 2.17±0.76 and 1.14±0.84 respectively (P=0.0003; Fig. 1C). The mean delta Ht z score was 0.32±0.58 in the CD vs 0.74±0.65 in the MAH group, which was significantly better in MAH (P=0.049). The mean delta BMI z score was −0.94±0.62 in the CD group and −1.04±1.0 in the MAH group (P=0.74; Fig. 1D).

We divided each group of patients into three categories, depending on their pubertal status: Tanner 1, Tanner 2–3, and Tanner 4–5. The mean delta Ht z scores in CD vs MAH were 0.51±0.35 vs 1.03±0.78 for Tanner 1 (P=0.16); 0.08±0.66 vs 0.83±0.40 for Tanner 2/3 (P=0.024); and 0.07±0.30 vs −0.01±0.07 for Tanner 4/5 (P=0.59) (Fig. 1E).

There was a strong positive correlation between BMI z score at surgery and the delta Ht z score (r=0.69, P=0.0012) in the MAH group but not in the CD group (r=0.19, P=0.44). The correlation of the delta BMI z score with delta Ht z score also showed a strong correlation in the MAH group (r=−0.67, P=0.002) but not in the CD group (r=−0.18, P=0.48) (Fig. 1F). Bone age z score was 0.8±2 and 0.6±1.4 in the MAH and CD group respectively (P=0.64), presented previously (Lodish et al. 2014).

For patients in Tanner categories 1–4 at surgery, the mean annual growth velocity was 10.47±2.69 cm in the MAH group vs 7.35±4.06 cm in the CD group (P=0.017). The mean IGF1 z score after surgery was 0.40±1.90 vs −0.77±1.33 for the MAH and CD patients respectively (P=0.050). When we excluded from the analysis the five MAH patients who are positive for a PRKARIA mutation (patients that could have Carney complex, and thus increased IGF1 levels), we found a significant difference in the post-surgery IGF1 z score, which was 0.98±2.03 in the MAH group vs −0.77±1.33 in the CD group (P=0.012). None of the patients in this analysis received growth hormone (GH) or thyroid hormone treatment.

This is the first study to compare, after a curative surgical procedure, the growth of pediatric patients with...
two forms of CS: CD and MAH. Our findings show that generally patients with MAH demonstrate better post-operative growth. There are several mechanisms that could explain the above observation.

First, the surgery can have a direct effect on the pituitary somatotrophs. In cases where the ACTH-secreting pituitary adenoma requires extensive surgical exploration, it is likely that the remaining pituitary cells will lose some of their function. Also, it is likely that the ACTH-producing tumor has a pressure effect on the somatotrophs that indirectly impairs the ability of the cells to produce GH.

Another reason is related to the direct adverse effects that the glucocorticoids have on the skeleton. It is possible that CD patients, who tend to be older, are exposed for a longer period of time to glucocorticoids, suffer vertebral fractures more frequently, and thus their skeleton and, hence their overall growth potential, is more affected. Moreover, patients with MAH can have cyclical forms of CS (Batista et al. 2007, Stratakis 2012), with hypercortisolism only intermittently present and an overall milder form of CS.

It is also possible that patients with CD are exposed to higher doses of glucocorticoids than what they need during their first 12 months of recovery. Although our group has shown that 75% of patients with CD should not require any hydrocortisone replacement by 14 months after surgery, and their glucocorticoids should be tapered starting after the first 6 months (and sometimes even sooner; Lodish et al. 2012), several patients are maintained on routine replacement for much longer, although the patients in the present study were all followed under our routine replacement doses, as described by Lodish et al.
We have recently shown that patients with CD may, in some cases, have advanced bone age due to their ACTH-stimulated adrenal androgen production and the latter’s increased aromatization (Lodish et al. 2014), as well as their increased obesity and adiposity (London et al. 2014) and tendency to have higher insulin resistance (London et al. 2014) than those with MAH, especially those with PRKAR1A mutations (London et al. 2014). Thus, it is also possible that patients with CD would have decreased postoperative growth rate as a function of their advanced skeletal maturation compared with that of patients with MAH. Although this may be true in general, in the subgroup of patients included in this study, the degree of skeletal maturity at surgery was not most likely a factor, because the bone age $z$ scores were $0.8 \pm 2$ and $0.6 \pm 1.4$ in the MAH and CD groups respectively ($P = 0.64$).

In addition, the patients with the greatest improvement in their BMI values had better growth after cure. This is probably because the patients with severe obesity represent the most affected patients with CS, who also get the most benefit after cure. Whether the final adult Ht compared with their target Ht is also compromised remains to be seen.

Another possible mechanism to explain our findings may be the related to the fact that CS is associated with GH suppression (Frantz & Rabkin 1964, Krieger & Glick 1972, Magiakou et al. 1994b). Previous studies have shown that longer duration and higher degree of hypercortisolism lead to greater GH suppression (Frantz & Rabkin 1964, Krieger & Glick 1972). The GH secretion profile was abnormal even 1 year after cure of CS in a study done previously at NIH (Magiakou et al. 1994b). Some of our patients with MAH also have Carney complex and germline mutations in $PRKAR1A$ gene (Stratakis et al. 2001). Carney complex can be associated with GH excess (Stratakis et al. 2001, Boikos & Stratakis 2006, Bertherat et al. 2009). Clinically apparent acromegaly in Carney complex occurs mostly in young adulthood (Stratakis et al. 2001, Boikos & Stratakis 2006, Bertherat et al. 2009), but it is possible that abnormal GH secretion exists in early childhood (Boikos & Stratakis 2006) and this is manifested in our patients with MAH as an earlier recovery of GH secretion than one would expect. However, even when we excluded the subset of patients with $PRKAR1A$ mutations, the MAH patients still had higher IGF1 $z$ scores after cure when compared with CD patients.

**Figure 1**
(A) Baseline height $z$ scores (left) and BMI $z$ scores (right) in CD and MAH at time of surgery. (B) Before and after surgery mean height $z$ score in CD (left) and in MAH (right); *$P=0.03$ and **$P=0.0002$. (C) Before and after surgery mean BMI $z$ score in CD (left) and in MAH (right); both groups improved significantly; *$P<0.0001$ and **$P=0.0003$. (D) Mean delta height $z$ score in CD and MAH group (left) and mean delta BMI $z$ score in CD and MAH group (right); **$P=0.049$. (E) Delta height $z$ score between CD and MAH when compared for the same Tanner stage; *$P=0.024$ between Tanner II–III group of CD and MAH. (F) Correlation of delta height $z$ score with delta BMI $z$ score in CD and MAH. The open squares represent MAH, with the dashed least squares fitted line; the closed circles represent CD, with the solid least squares fitted line; correlation in MAH $r=-0.67$, with $P=0.02$. 

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Finally, this study demonstrated that patients with MAH grow significantly better after surgery, even when compared with a group of CD patients of the same Tanner stage at the time of surgery (Dupuis et al. 2007). A limitation of our study is that we do not have GH secretion profiles after surgery and adult final Ht in these patients.

In conclusion, there are important messages from these clinical observations: patients with MAH are less likely to need GH therapy after surgery for their CS. On the other hand, physicians should monitor patients with CD very closely and have a low threshold for considering treatment with GH to improve their final adult Ht. Finally, every effort for improvement in BMI with lifestyle modification could potentially improve growth of children with CS after they are cured.

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
E Gourgari performed most of the data collection described in the manuscript and prepared the manuscript. M Lodish is currently the principal investigator for the clinical protocols. M Keil, C Lyssikatos, and E Belyavskaya participated in the clinical care of the patients. R Wesley did the statistical analysis. S Hill was responsible for the reading and interpretation of bone age films of the patients. S M De La Luz and P Xekouki participated in the genetic analysis of the patients. C A Stratakis was the principal investigator of the clinical protocol until recently, saw all the patients, and his NIH Intramural Grant provided all of the funding for this project; he also supervised the presentation of results, design of figures, and assisted in writing this manuscript.

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