

# An Assessment Of The Hypothalamic-Pituitary-Adrenal Axis In Children With Prader-Willi Syndrome

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Authors have nothing to disclose

## Introduction - Aim

In children with Prader-Willi Syndrome (PWS), hypothalamic dysfunction plays a key role in the development of aberrant energy regulation and obesity, sleep-related breathing disorders, hypogonadism and impaired linear growth.

Dysfunction of hypothalamic-pituitary-adrenal (HPA) axis may contribute to the high incidence of sudden death. The prevalence and the extent of the dysfunction of HPA axis remain unclear. The aim of the study was to explore the function of HPA axis in children with PWS.

## Methods

Thirty-eight children with PWS, underwent insulin tolerance test (ITT) or glucagon stimulation test as part of their assessment before commencing growth hormone (GH) treatment. Cortisol and GH were measured at 0, 15, 30, 45, 60, 90 and 120 minutes in relation to insulin or glucagon administration. Either cortisol peak of  $\geq 550$  nmol/L or cortisol increase from baseline (increment) of  $\geq 250$  nmol/L were considered as adequate cortisol responses. GH peak of  $\geq 6.7$   $\mu\text{g/L}$  was considered an adequate GH response.

## Results

### Characteristics of the 31 children

|                     | All children       | Glucagon test       | ITT                 | <i>p</i> |
|---------------------|--------------------|---------------------|---------------------|----------|
| Number of patients  | 38                 | 27                  | 11                  |          |
| Sex (males/females) | 12/26              | 11/16               | 1/10                | 0.059    |
| Age (years)         | 2.71 (0.58, 15.57) | 2.29 (0.58, 4.67)   | 6.96 (4.08, 15.57)  | <0.0001  |
| Height SDS          | -2.46 (-6.95, 0.8) | -2.53 (-5.68, -0.8) | -2.38 (-6.95, 0.08) | 0.810    |
| BMI SDS             | 0.11 (-2.19, 4.38) | -0.82 (-2.19, 3.0)  | 2.68 (-0.76, 4.38)  | <0.0001  |

Values: median (range)

Table 1

### Peak Cortisol

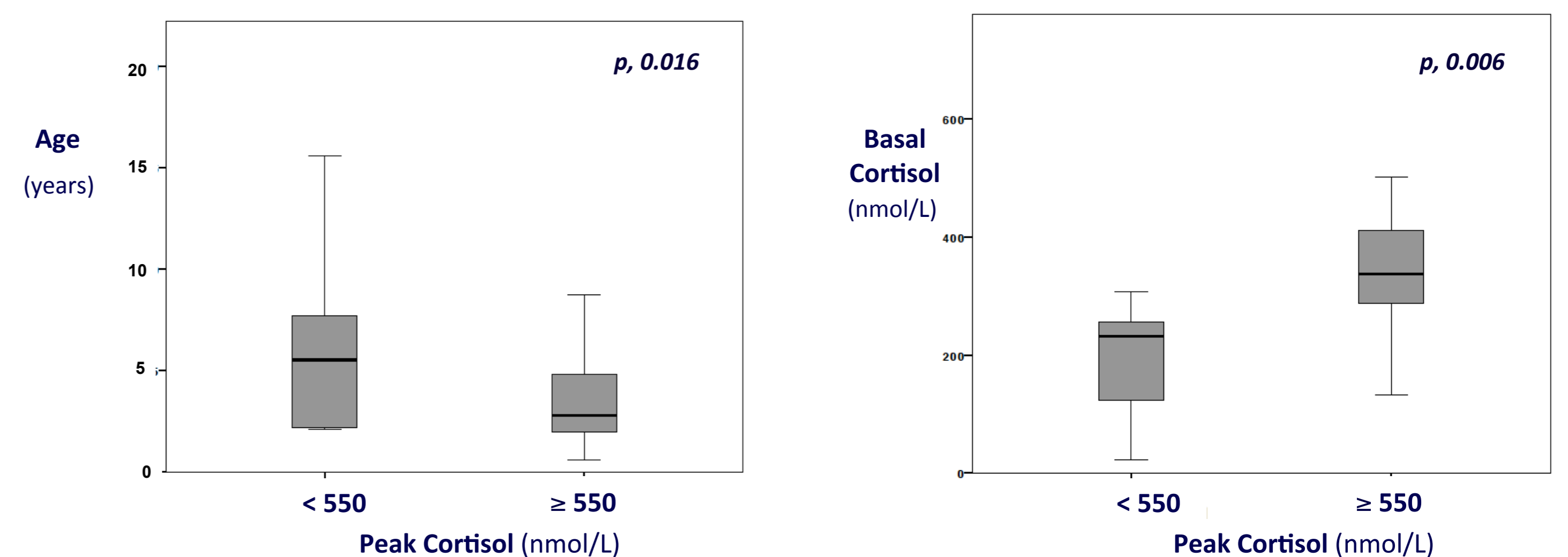


Fig 6 & 7. Six children (16%) had peak cortisol levels below the cut-off value of 550 nmol/L. These children were older and had lower baseline cortisol levels than those (n, 32) with peak cortisol levels  $\geq 550$  nmol/L.

### Cortisol Response

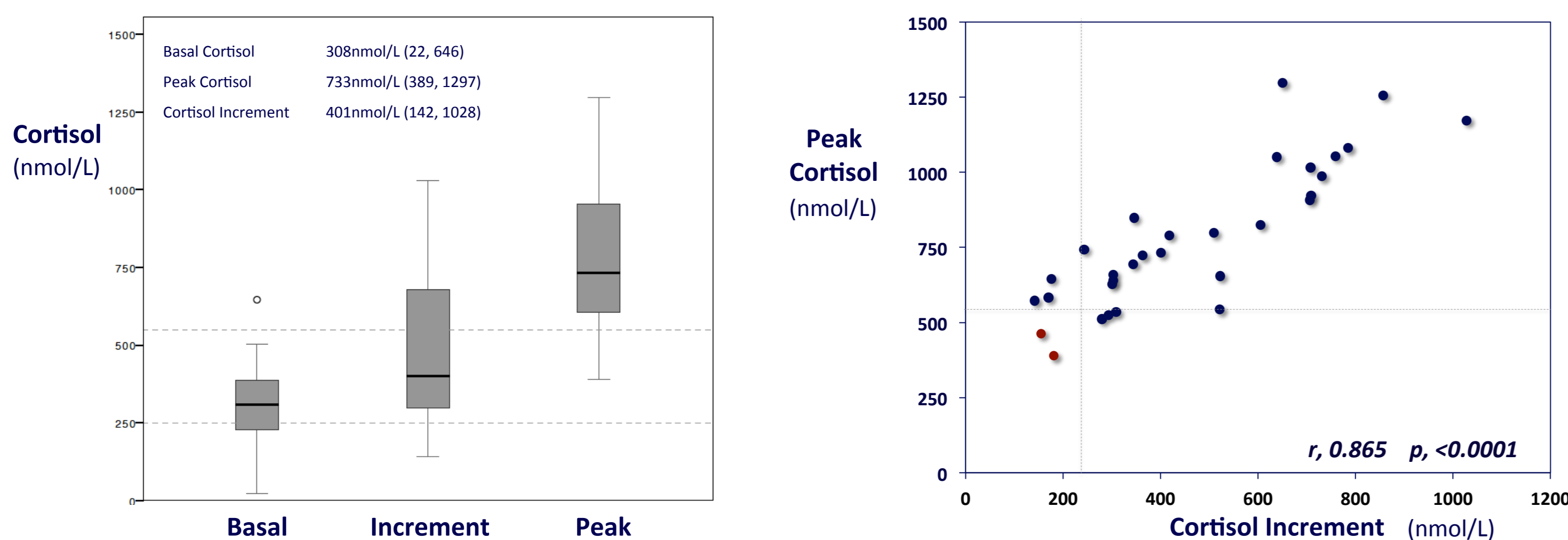


Fig 1. Basal cortisol and cortisol increment and peak cortisol after insulin or glucagon administration.

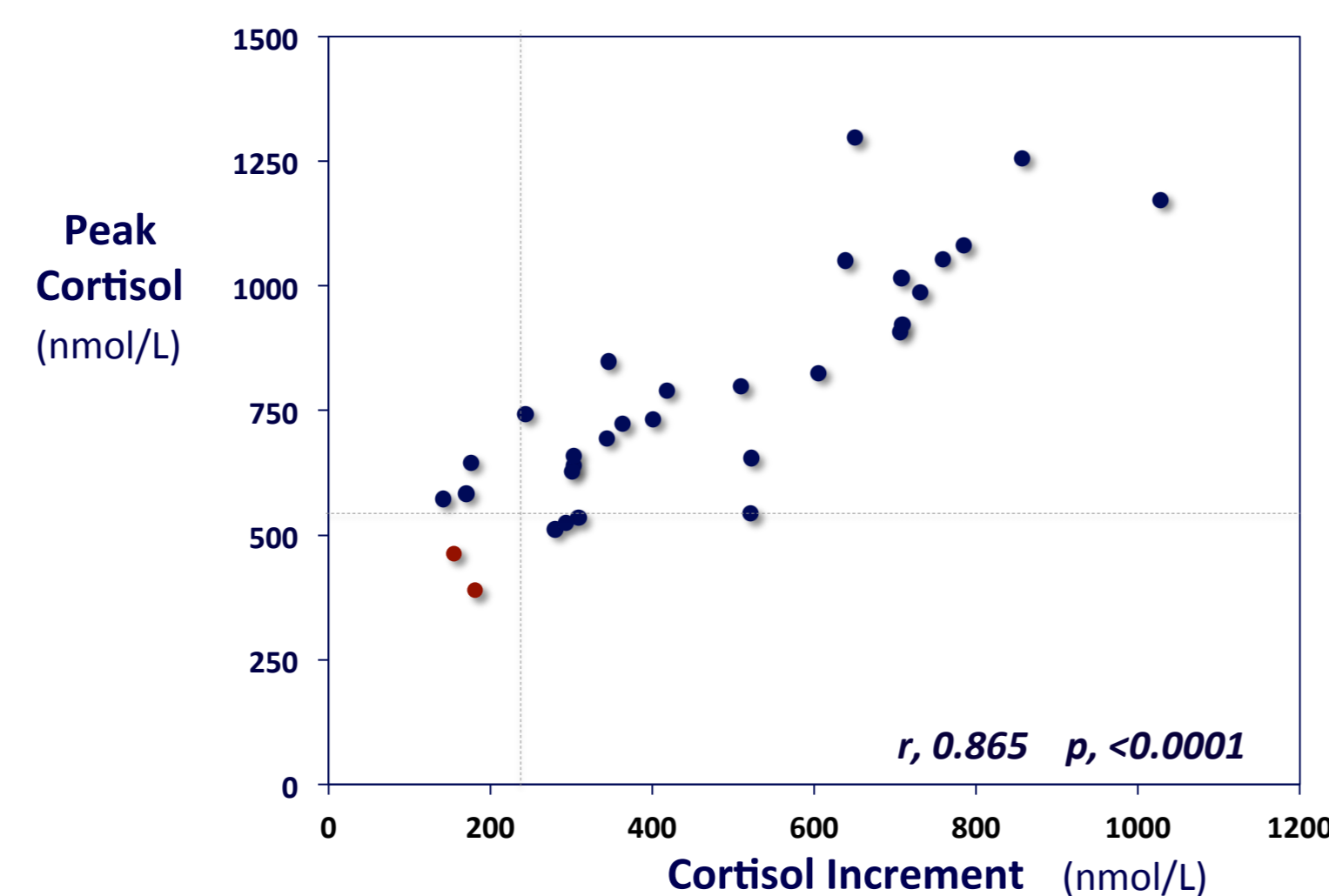


Fig 2. The majority of the children (36/38, 94%) showed adequate cortisol response.

### BMI and Cortisol Response

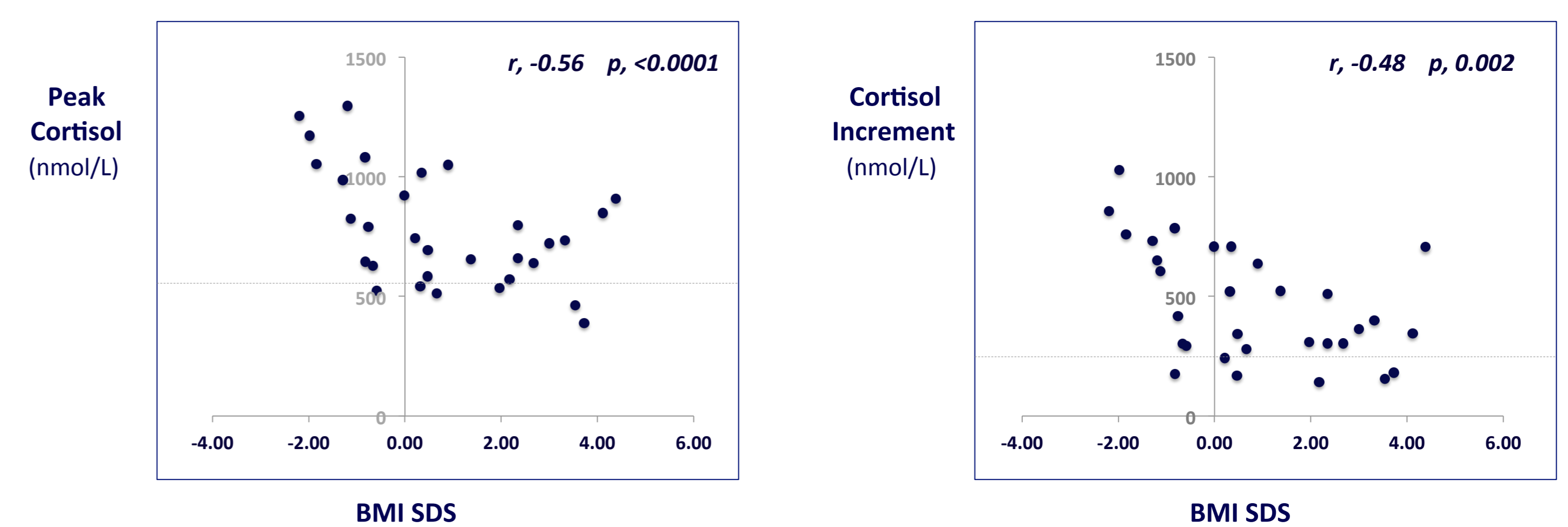


Fig 8. Negative correlation between cortisol peak and BMI SDS

Fig 9. Negative correlation between cortisol increment and BMI SDS.

### Children with insufficient Cortisol response

|                    | Subject 1 (red) | Subject 2 (blue) |
|--------------------|-----------------|------------------|
| Age                | 15.57 years     | 7.7 years        |
| Sex                | female          | female           |
| Height SDS         | -2.38           | -4.28            |
| BMI SDS            | 3.54            | 3.23             |
| Test               | ITT             | ITT              |
| Basal Cortisol     | 308 nmol/L      | 208 nmol/L       |
| Peak Cortisol      | 463 nmol/L      | 389 nmol/L       |
| Cortisol Increment | 155 nmol/L      | 181 nmol/L       |

Table 2. Clinical and biochemical parameters of the 2 children with insufficient cortisol response.

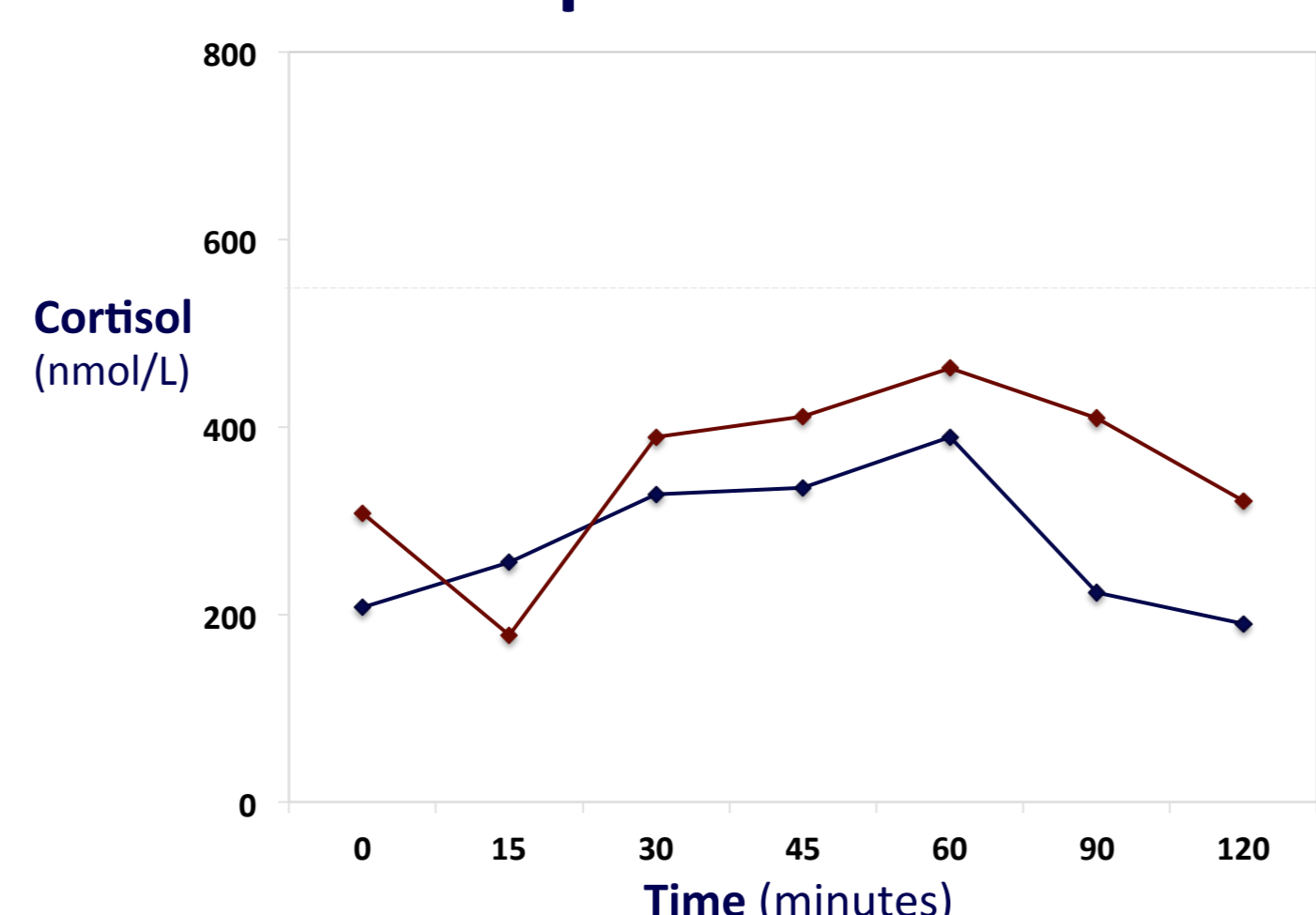


Fig 3. Cortisol levels during ITT of the 2 children with insufficient cortisol response.

### Growth Hormone Response and Cortisol Response

|                     | GH Deficient (GHD) | GH Sufficient (Non-GHD) | <i>p</i> |
|---------------------|--------------------|-------------------------|----------|
| Number of patients  | 26 (68%)           | 12 (32%)                |          |
| Sex (males/females) | 8/18               | 4/8                     | 0.58     |
| Height SDS          | -2.60 (-6.95, 0.8) | -2.04 (-4.18, -0.4)     | 0.372    |
| BMI SDS             | 0.27 (-1.98, 4.38) | 0.35 (-2.19, 4.11)      | 0.827    |

Table 3. Characteristics of the children with (71%) and those without (29%) Growth Hormone deficiency.

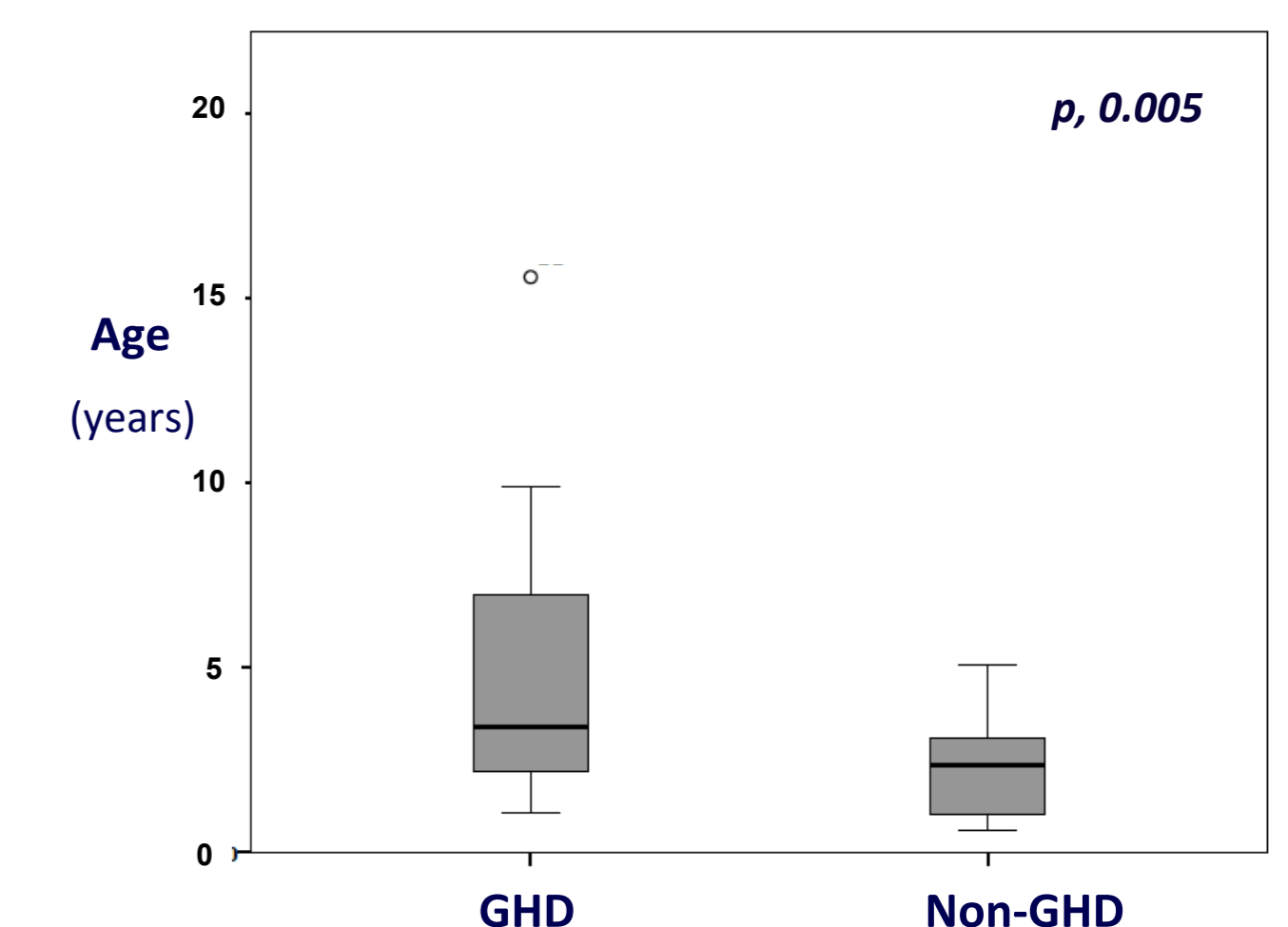


Fig 10. The children with GHD were older than those with sufficient GH response after ITT/Glucagon test.

### Cortisol Response and Age

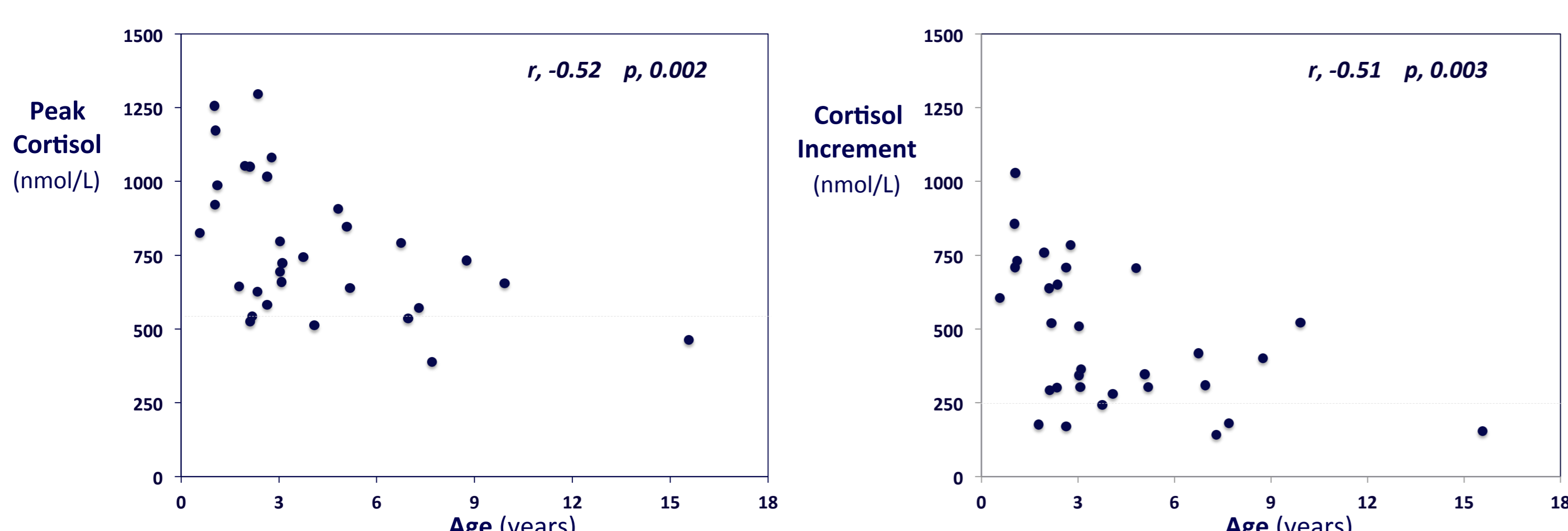


Fig 4. Negative correlation between peak cortisol levels and age.

Fig 5. Negative correlation between cortisol increment and age.

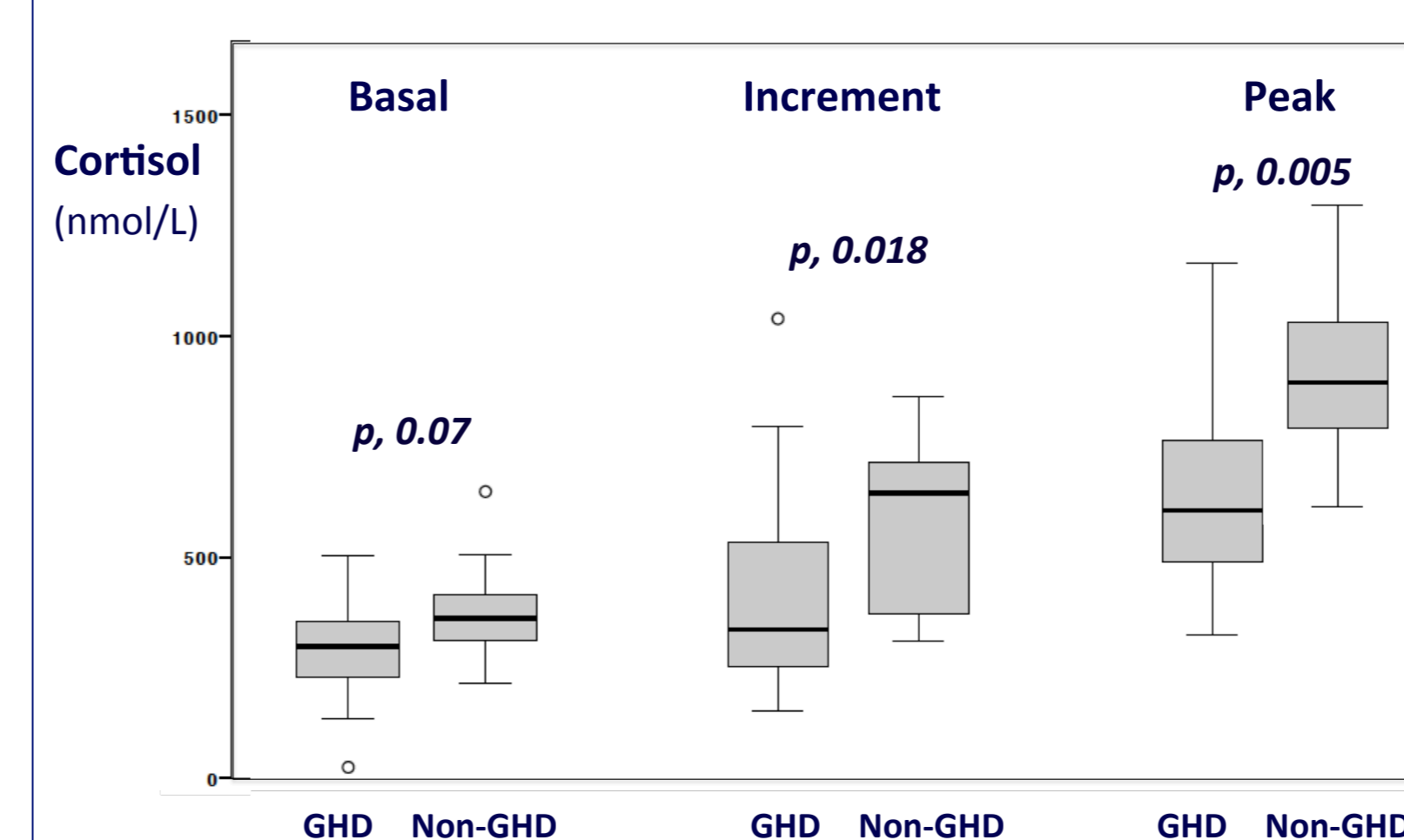


Figure 11. Basal cortisol, cortisol increment and cortisol peak of the children with and those without GHD. Children with GHD had lower cortisol peak levels and lower cortisol increment.

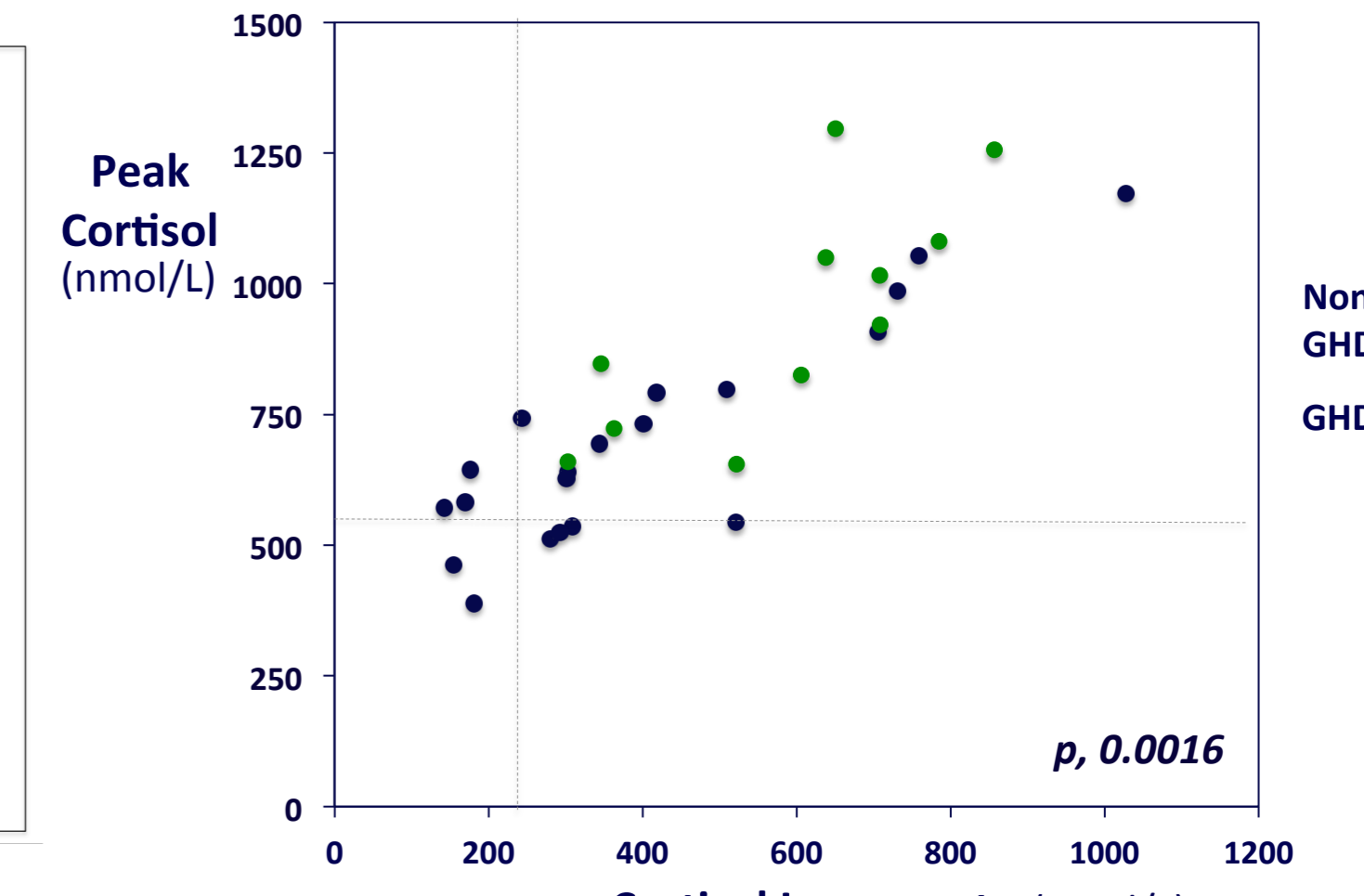


Figure 12. All 12 children with sufficient GH response had cortisol peak levels  $\geq 550$  nmol/L and cortisol increment  $\geq 250$  nmol/L

## Conclusion

- The majority of children with PWS showed a normal function of HPA axis.
- Although cortisol secretion decreases continuously with age, age-specific peak cortisol thresholds are required.
- The lower cortisol levels in those with GH deficiency may reflect a more generalised hypothalamic dysfunction.