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Should short children born small for gestational age (SGA) with a distance to target height (DTH) <1 SDS be excluded from growth hormone (GH) treatment?

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3 1 **Should short children born small for gestational age (SGA) with a distance to target height**
4 **(DTH) <1 SDS be excluded from growth hormone (GH) treatment?**
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3 1 **Abstract**
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5 2 **Context:** The criteria for starting Growth Hormone (GH), an approved treatment for short children
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7 3 born small for gestational age (SGA), differ between Europe and the USA. One European requirement
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9 4 for starting GH, a distance to target height (DTH) of ≥ 1 SDS, is controversial.
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14 6 **Objective:** To investigate the influence of DTH on growth during GH treatment in short SGA
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16 7 children, and to ascertain whether it is correct to exclude children with a DTH < 1 SDS from GH.
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21 9 **Patients:** A large group of short prepubertal SGA children (baseline $n=446$; 4 years GH $n=215$).
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25 11 **Measurements:** We analysed the prepubertal growth response during 4 years of GH. We investigated
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27 12 the influence of the continuous variable DTH SDS on growth response, and a possible DTH SDS cut-
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29 13 off level below which point the growth response is insufficient.
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33 14 **Results:** Height gain SDS during 4 years of GH showed a wide variation at every DTH SDS level.
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35 15 Multiple regression analyses demonstrated that, after correction for other significant variables, an
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37 16 additional DTH of 1 SDS resulted in 0.13 SDS more height gain during 4 years of GH. We found no
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39 17 significant differences in height gain below and above certain DTH SDS cut-off levels.
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43 18 **Conclusions:** DTH SDS had a weak positive effect on height gain during 4 years of GH, while
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45 19 several other determinants had much larger effects. We found no support for using any DTH cut-off
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47 20 level. Based on our data, excluding children with a DTH < 1 SDS from GH treatment is not justified.
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1 Introduction

2 Small for gestational age (SGA) is defined as a birth weight and/or birth length below -2.0 standard
3 deviation score (SDS) (1). Approximately 10% of the children born SGA do not show spontaneous
4 catch-up growth during the first years of life and will have persistent short stature (2-4). These short
5 SGA children can be effectively and safely treated with growth hormone (GH) (5-7). Nowadays, GH
6 is an approved treatment for short stature in children born SGA in the United States (Food and Drugs
7 Administration, 2001) and Europe (European Medicines Agency, 2003). The criteria to start GH
8 differ between these continents (5); the European requirement of a distance to target height (DTH) of
9 at least 1 SDS is not used in the United States.

10

11 Since reduced size at birth may result from any foetal, maternal, placental or demographic influence,
12 SGA children comprise a heterogeneous group with a broad spectrum of clinical features. Although
13 the total group of SGA children with persistent short stature benefit from GH, there is a wide variation
14 in the response to GH treatment. Many studies have attempted to find variables in short SGA children
15 predicting the growth response to GH in the first year (8), until the onset of puberty (9), and up to
16 adult height (7, 9, 10). Important variables appeared to be: gender, age at start of GH treatment, GH
17 dose, height at start, bone age delay at start, target height (TH), and in a Swedish study also the
18 difference between height SDS at start and the mid-parental height SDS (10, 11). Although it might
19 be likely that short children with a small distance to target height (DTH; TH SDS – height SDS at
20 start) have a lower growth response to GH, the European criterion for starting GH in short SGA
21 children with a DTH SDS>1 is not evidence-based and is subject of continuous discussion.

22

23 The aim of our study was to ascertain whether it is justified to exclude children with a DTH SDS<1
24 from GH treatment. We had the opportunity to investigate the growth response in a large group of
25 prepubertal short SGA children treated with GH. We investigated the influence of the continuous
26 variable DTH SDS on growth response, and we studied a possible DTH SDS cut-off level, below
27 which point the growth response is insufficient.

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1 **Patients and methods**

2 *Subjects*

3 The study cohort consisted of 446 short children born SGA, who were treated with GH in four trials
4 (trials 1 (12), 2 (13), 3 (14) and 4 (15)), of which data have been published. Children were included in
5 the present study if they met the following criteria: A) birth length and/or birth weight SDS for
6 gestational age below -2.0 (16); B) height SDS for calendar age (CA) at start (17) below -2.0 (trials 1
7 and 2) or -2.5 (trials 3 and 4); C) height velocity SDS for CA below zero to exclude children with
8 spontaneous catch-up growth; D) CA at start of 3 yr or older; E) prepubertal stage at start of GH
9 treatment and F) available parental height. Children were excluded if there was a complicated
10 neonatal period, or signs of severe asphyxia (defined as Apgar score 3 or less after 5 minutes),
11 endocrine or metabolic disorders, chromosomal disorders, growth failure caused by other disorders
12 (emotional deprivation, severe chronic illness, or chondrodysplasia), or syndromes (except for Silver-
13 Russell syndrome), as well as children who were using or had used medication that could interfere
14 with growth. The studies were in accordance with the Declaration of Helsinki and approved by the
15 Medical Ethics Committees of the participating centres. Written informed consent was obtained from
16 the parents or guardians of each participating child.

18 *Study design*

19 All children were treated with GH subcutaneously once daily at bedtime. Depending on the study
20 design, the GH dose was 1 mg/m²/day (~0.033 mg/kg) or 2 mg/m²/day (~0.066 mg/kg). Every three
21 months the GH dose was adjusted to the calculated body surface area. The growth responses of the
22 prepubertal children after 1 and 4 years of GH treatment were analysed. We investigated data from the
23 total group, as well as from three subgroups according to the distance to target height at start of GH
24 treatment: DTH SDS<1, DTH SDS1-2 and DTH SDS>2.

1 *Measurements*

2 At the start and three monthly during GH treatment, standing height, weight and Tanner stage were
3 determined, as described elsewhere (12). Body mass index (BMI) was calculated as weight divided by
4 height squared (kg/m²). Height, TH, BMI and sitting height/height ratio (SH/H) were expressed in
5 SDS, adjusting for age and gender according to Dutch reference data (17). TH was calculated as TH =
6 [(maternal height + parental height + 13) / 2 + 4.5] for boys and TH = [(maternal height + parental
7 height - 13) / 2 + 4.5] for girls (18). Target height range (THR) was defined as TH SDS +/- 1.3 (17).
8 Distance to target height SDS (DTH SDS) was determined as TH SDS minus height SDS at start.
9 Bone age (BA) was determined according to the Greulich and Pyle method (19). Bone age delay was
10 calculated calendar age (CA) minus BA in years. To correct for differences in GH dose over time, the
11 mean GH dose during 1 or 4 years of GH treatment was used, instead of the GH dose at start of the
12 study. Prepubertal stage was defined as Tanner breast stage 1 for girls and testicular volume less than
13 4 ml for boys (20).

14 *Assays*

15 At baseline and yearly during GH treatment, blood samples were taken after an overnight fast. After
16 centrifugation, all samples were frozen (-80°) until assayed. Insulin-like growth factor-I (IGF-I) and
17 Insulin-like growth factor-binding protein-3 (IGFBP-3) were measured in one laboratory using
18 specific radio immunoassays (RIAs), as previously described (21). Serum levels of total IGF-I and
19 IGFBP-3 were expressed in SDS, adjusting for age and gender, using reference values for healthy
20 children of normal stature determined in the same laboratory (22).

21 *Statistics*

22 Analyses were carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows.
23 Results are expressed as the median (interquartile range), unless indicated otherwise. One-Sample t-
24 test was used to compare results, expressed as SDS, with zero SDS (mean value for age-matched
25 healthy references). We used the Pearson Chi-Square test to determine differences in categorical
26 variables between the three subgroups. Correlations were tested with the Pearson correlation test. To

1 evaluate the relative contribution of several determinants to the dependent variable height gain SDS,
2 we performed multiple linear regression analyses. The potential determinants were: 1) initial
3 characteristics: gender, birth weight SDS, birth length SDS, gestational age, TH SDS, 2) baseline
4 characteristics at start of GH treatment: CA, height SDS, weight SDS, BMI SDS, SH/H ratio SDS,
5 IGF-I SDS, IGFBP-3, BA delay, DTH SDS and 3) treatment characteristics: mean GH dose. A known
6 interaction term between IGFBP-3 SDS and GH dose was added to the model (9). The best fitting
7 models illustrating the contribution of DTH SDS are shown. Statistical significance was defined as
8 $P < 0.05$.

10 **Results**

11 The group characteristics and growth results are shown in Table 1. The total group comprised only
12 those children who remained prepubertal throughout the study period. The median height SDS at start
13 of GH was -3.02 . The median TH SDS was significantly lower than that of the normal population.
14 The median height gain SDS during the first year was 0.86 , and during 4 years 1.89 . After 4 years of
15 GH treatment, 83% of all children had reached a height in the normal range (height SDS > -2); the
16 median height SDS at that time was -1.19 .

18 *Correlations and multiple regression analyses*

19 The continuous variable DTH SDS appeared to be negatively correlated with height SDS after 4 years
20 of GH treatment ($R = -0.18$, $P < 0.01$, Figure 1). This indicates that a larger DTH SDS was correlated
21 with a shorter height SDS after 4 years of GH, however, the obtained height SDS showed a wide
22 variation between the children. Comparing the three subgroups according to the DTH SDS (DTH
23 SDS < 1 , DTH SDS $1-2$ and DTH SDS > 2) showed a higher percentage of children with a height in
24 the normal range (height SDS > -2) when the DTH SDS was smaller (not significant, Figure 1).

26 Since an achieved height SDS after GH treatment depends on the height SDS at start, it is more
27 interesting to investigate height gain SDS during treatment. We therefore studied the correlation

1 between DTH SDS and height gain SDS during GH treatment. The variable DTH SDS at start had a
2 significant, positive correlation with height gain SDS after 1 year ($R=0.32$, $P<0.01$) and after 4 years
3 of GH ($R=0.35$, $P<0.01$, Figure 2). During 4 years of GH, the height gain SDS showed a broad range
4 with a minimum of 0.34 SDS and a maximum of 4.09 SDS. Although our data demonstrated a
5 continuous, positive correlation between DTH SDS and height gain SDS, there was a wide variation
6 at each level of DTH SDS, without an appropriate cut-of level for DTH SDS.

7
8 To ascertain whether the correlation between DTH SDS and height gain SDS during 4 years of GH
9 also remains after correction for differences at baseline and known influencing variables, we
10 performed multiple regression analyses (Table 2). Model A ($P<0.01$) showed that gender, age at start,
11 height SDS at start and the interaction term between GH dose and IGFBP-3 SDS at start were
12 significant negative determinants of height gain SDS, whereas mean GH dose was a significant
13 positive determinant. DTH SDS at start instead of height SDS showed that DTH SDS had a regression
14 coefficient of $+0.13$ ($P<0.01$, Model B). The differences in R^2 in Model B compared to Model A
15 demonstrated that only 3% of the explained variation in height gain SDS was due to the effect of DTH
16 SDS.

17
18 In addition, we used DTH SDS as a categorical variable to investigate whether a DTH SDS below a
19 certain cut-off level resulted in significantly less height gain during 4 years of GH (Table 2). We
20 found that a $DTH\ SDS<1$ compared to $DTH\ SDS\geq 1$ did not result in a significantly different height
21 gain ($P<0.01$, Model D). We also compared the growth response of all children with a $DTH\ SDS<2$
22 with that of the $DTH\ SDS\geq 2$ subgroup. The last model did not show a significantly different height
23 gain between children with a $DTH\ SDS<2$ and children with a $DTH\ SDS\geq 2$ ($P<0.01$, Model E).

1 Discussion

2 Our study showed a weak positive correlation between the continuous variable DTH SDS and gain in
3 height SDS during 4 years of GH, in short, prepubertal children born SGA. Each additional DTH SDS
4 resulted in only 0.13 SDS more gain in height during 4 years of GH, while several other significant
5 determinants had much larger effects. The growth response showed a wide variation across the entire
6 DTH SDS range and did not support any cut-off level. Our results demonstrate that the European cut-
7 off level of a DTH SDS \geq 1 is not justified; using this criterion will exclude children who can also
8 benefit from GH treatment.

9
10 The growth response, a gain in height SDS during 4 years of GH, was significantly positively
11 correlated with DTH SDS, **in line with previous studies (10, 11)**. After adjustment for gender, age at
12 start, GH dose, and the interaction term between GH dose and IGFBP-3, 1 SDS smaller DTH was
13 associated with only 0.13 SDS less height gain, equivalent to approximately 0.8 centimetre difference
14 during 4 years of treatment. The total model explained 40% of the variance in height gain during 4
15 years of GH, but DTH SDS was responsible for only 3% of this gain. Thus, although DTH SDS
16 influenced the height gain, it was much less important than several other determinants. **Moreover,**
17 **there was a large variation in height gain SDS independent of DTH SDS, meaning that also children**
18 **with a large DTH SDS response differently to GH treatment. This variation can not be explained with**
19 **the nowadays knowledge and needs further research.**

20
21 We also investigated if children below and above various DTH SDS cut-off levels responded
22 differently to GH treatment. The scatter plots of height gain SDS during 4 years of GH treatment
23 showed no obvious cut-off level for DTH SDS. After adjusting for other influencing variables, we
24 neither found a significant difference in height gain between children with a DTH SDS $<$ 1 and
25 children with a DTH SDS \geq 1, nor between children with a DTH SDS $<$ 2 and children with a DTH
26 SDS \geq 2.

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3 1 Another objective to evaluate the benefit of GH treatment could have been reaching a height within
4
5 2 the target height range (THR). But since, per definition, children with a DTH SDS<1 have a baseline
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7 3 height in their THR, it is inappropriate to use this objective to investigate the influence of DTH
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9 4 SDS on growth response. With regard to TH SDS it is worth noting, however, that TH is a calculation
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11 5 including height of child's father and mother; if one parent is very short, the TH SDS will be low and
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13 6 therefore the DTH SDS will be lower too. This does not necessarily mean that the child's growth
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15 7 potential is determined by the height of the shortest parent. Although children were excluded from
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17 8 GH treatment when they had major dysmorphic features, children with a smaller DTH SDS are more
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19 9 likely to have genetic abnormalities that restrict prenatal and/or postnatal growth and result in short
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21 10 stature in parents and child. On the other hand, there is increasing evidence that children with genetic
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23 11 variations such as IGF-1 receptor haploinsufficiency and d3-GH receptor polymorphisms do respond
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25 12 well to GH treatment (23-26).
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31 14 We did not find a justification for any cut-off level based on DTH SDS, including the European
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33 15 requirement of a DTH SDS \geq 1. By using this requirement, children will be excluded who appeared to
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35 16 benefit from GH treatment like children with a larger DTH SDS. The wide individual variation in
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37 17 growth response suggests that treatment plans should be more individualised. Instead of using an
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39 18 arbitrary cut-off level for DTH SDS, it seems more appropriate to use growth prediction modelling to
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41 19 institute individualized GH treatment.
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1 **Table 1.** Clinical characteristics of the total group of prepubertal short SGA children

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Start of GH treatment (prepubertal)	n	
Boys / girls	446	249 / 197
Birth weight SDS	443	-2.23 (-3.11 -1.60)*
Birth length SDS	325	-2.89 (-4.01 -2.17)*
Age (years)	446	6.65 (4.90 8.56)
Height SDS	446	-3.02 (-3.39 -2.61)*
TH SDS	446	-0.53 (-1.13 0.03)*
DTH SDS	446	2.43 (1.91 3.00)
Mother height SDS	446	-1.02 (-1.66 -0.19)*
Father height SDS	446	-0.99 (-1.70 -0.18)*
BMI SDS	446	-1.23 (-2.00 -0.63)*
SH/H ratio SDS	437	1.20 (1.34 2.02)*
IGF-I SDS	419	-1.23 (-2.00 -0.28)*
IGFBP-3 SDS	408	-1.21 (-1.82 -0.49)*
BA delay (years)	398	1.40 (0.74 2.10)*
Patients before introduction of DTH >1 SDS (%) #	446	402/446 (90%)
After 1 year of GH treatment (prepubertal)		
Height SDS	394	-2.18 (-2.66 -1.73)*
Height gain SDS (0 - 1 yrs)	394	0.86 (0.64 1.05)
After 4 years of GH treatment (prepubertal)		
Height SDS	215	-1.19 (-1.75 -0.64)*
Height gain SDS (0 - 4 yrs)	215	1.89 (1.53 2.30)
Height SDS \geq -2 (%)	215	179/215 (83%)
Height in TH range (%)	215	159/215 (74%)

18 Data expressed as median (interquartile range) unless written otherwise.

19 SDS, Standard Deviation Score; TH, Target Height; BMI, Body Mass Index; BA delay, calendar age – bone age;

20 SH/H ratio, sitting height / height ratio.

21 * P < 0.001 compared with zero SDS (median for age and height)

22 # Patients who were included before the introduction of the European requirements in 2005, including DTH \geq 1 SDS,
23 as a percentage of the total group of included patients.

1 **Table 2.** Multiple regression models for gain in height SDS during 4 years of GH

	Model A		Model B		Model C		Model D	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Constant	1.84	<0.01	1.70	<0.01	2.14	<0.01	2.12	<0.01
Gender #	-0.23	<0.01	-0.24	<0.01	-0.26	<0.01	-0.25	<0.01
Age at start in years	-0.12	<0.01	-0.10	<0.01	-0.13	<0.01	-0.12	<0.01
Height SDS at start	-0.10	0.10						
Mean GH dose mg/kg/day	0.54	<0.01	0.56	<0.01	0.61	<0.01	0.59	0.03
IGF-I SDS at start	-0.04	0.22	-0.03	0.29	-0.04	0.14	-0.04	0.19
IGFBP-3 SDS at start	0.19	0.11	0.19	0.11	0.16	0.18	0.15	0.19
GH dose*IGFBP3 SDS ^	-0.25	0.02	-0.25	0.02	-0.23	0.03	-0.23	0.03
Continuous variable								
Distance to TH SDS			0.13	<0.01				
Categorical variable								
DTH <1 SDS*					-0.22	0.33		
DTH <2 SDS*							-0.14	0.10
Overall		<0.01		<0.01		<0.01		<0.01
R square		0.37		0.40		0.36		0.36
R square adjusted		0.35		0.37		0.34		0.34

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4 All variables are at start of GH treatment, except for mean GH dose.

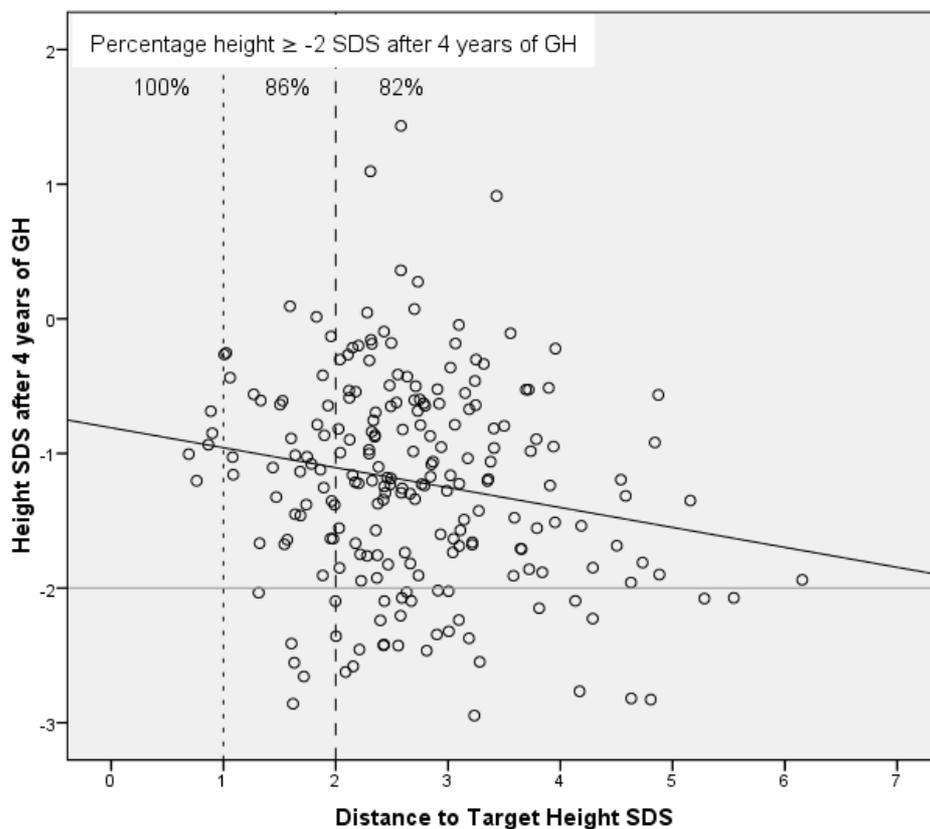
5 Not significant variables were BA delay, birth length SDS, birth weight SDS, gestational age and BMI SDS.

6 # Gender, Boy = 0 and girl = 1

7 ^ This interaction term indicates that the dose effect is related to the value of IGFBP-3 SDS at start. Because of the
8 negative coefficient of this term, the relation is: for lower values of IGFBP-3, the dose effect of GH is higher (9).

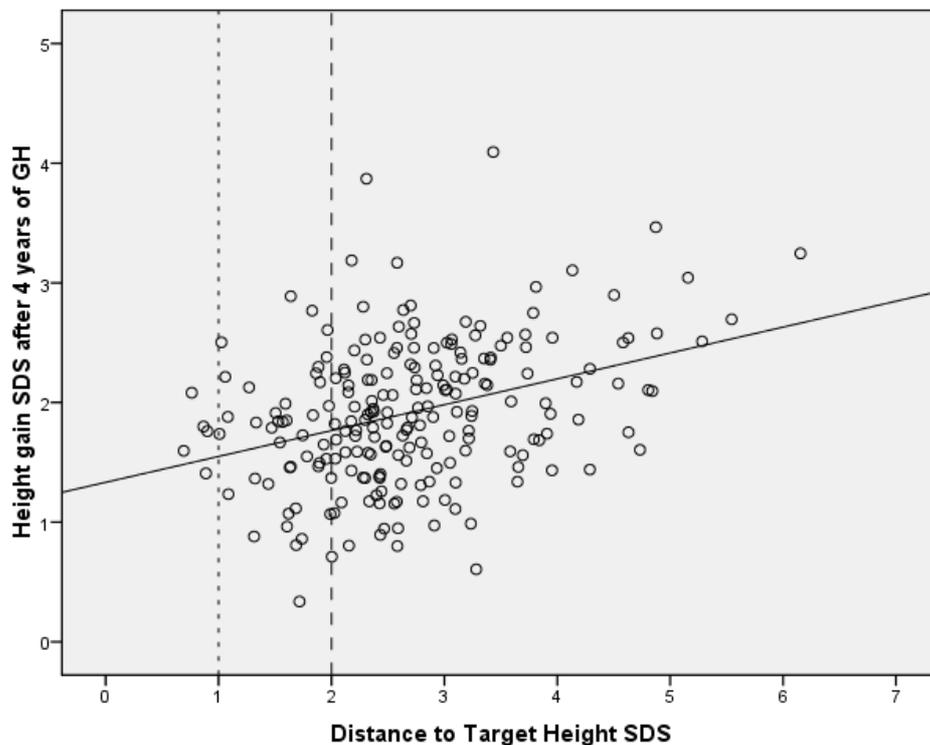
9 * DTH <1 SDS = 1 and DTH ≥1 = 0; DTH <2 SDS = 1 and DTH ≥2 = 0

1 **Figure 1.** Height SDS in relation to DTH SDS in prepubertal children after 4 years of GH



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4 Pearson correlation = -0.18, $R^2 = 0.03$, $P < 0.01$

5 **Figure 2.** Height gain SDS in relation to DTH SDS in prepubertal children after 4 years of GH



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6 Pearson correlation = 0.35, $R^2 = 0.12$, $P < 0.01$