

Predictors of Poor Response to Growth Hormone Therapy in Children with Short Stature - Evidence from Neural Prediction Model for Final Height

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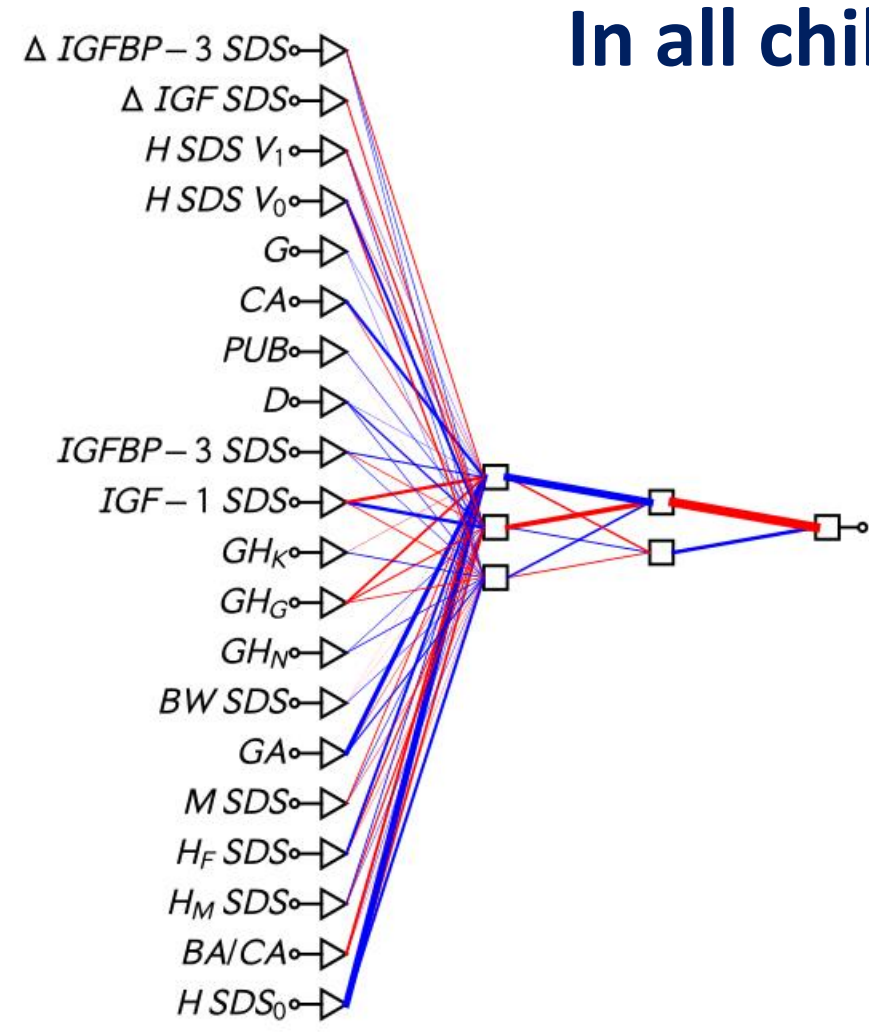
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Prediction of poor response to growth hormone (GH) therapy in children with short stature is an important issue for personalized approach to treatment. Recently, our research group has published prediction models derived with neural networks. The main predictors of final height (FH) in our model were: patient's height SDS at therapy onset ($H\ SDS_0$) and pre-treatment IGF-I and IGFBP-3 concentrations but not the results of GH stimulation tests; pre-treatment growth rate was also a significant variable.

The aim of present study is to analyze the main predictors of poor and good growth response to GH therapy in children with wide range of GH secretion.

Analysis comprised 133 children (89 boys) with short stature (101 with GH deficiency - GHD and 32 with idiopathic short stature - ISS), treated with GH up to FH.

In all children 20 auxological and hormonal parameters was assessed before treatment, in 1st year of therapy and at FH:

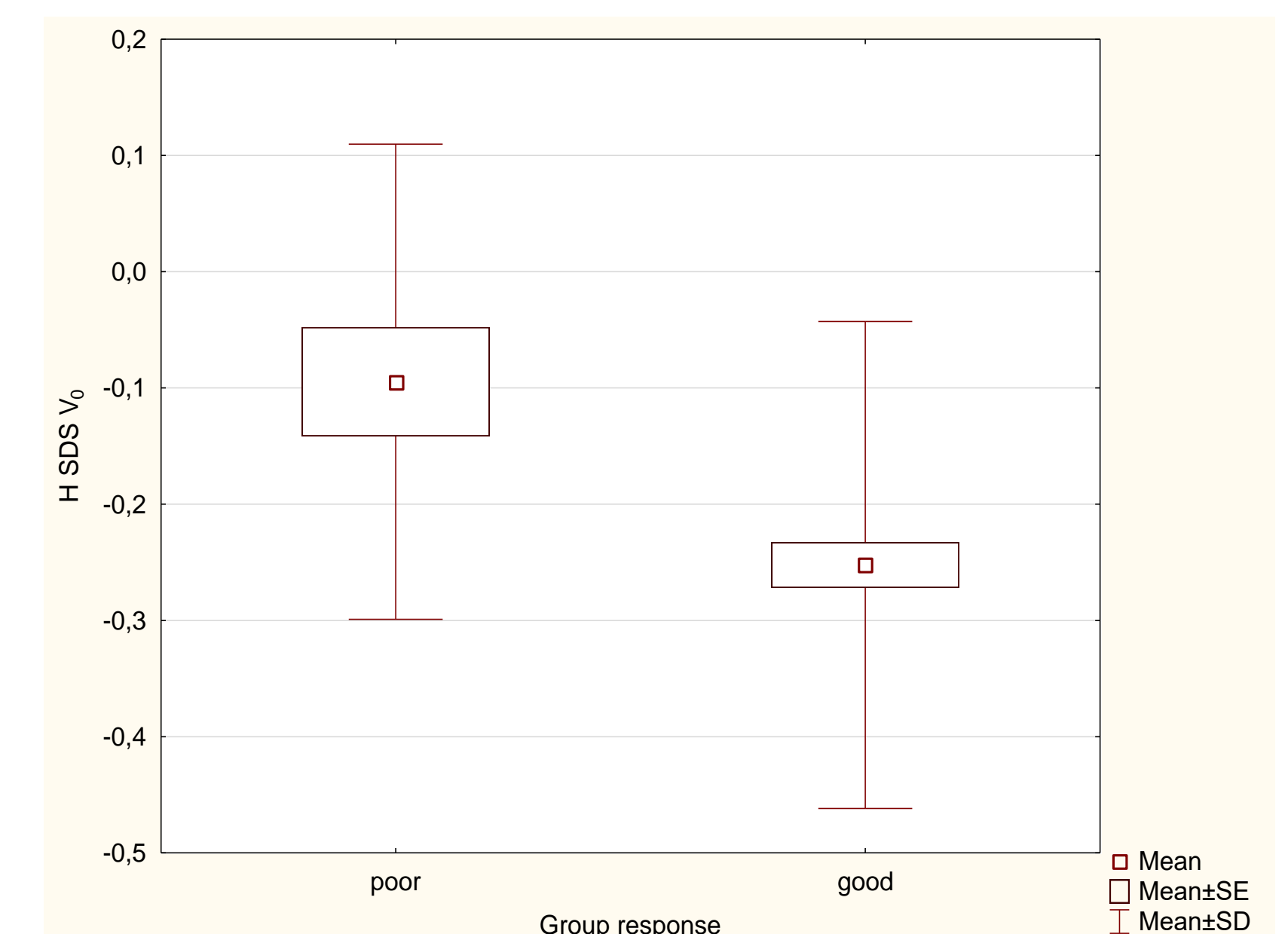
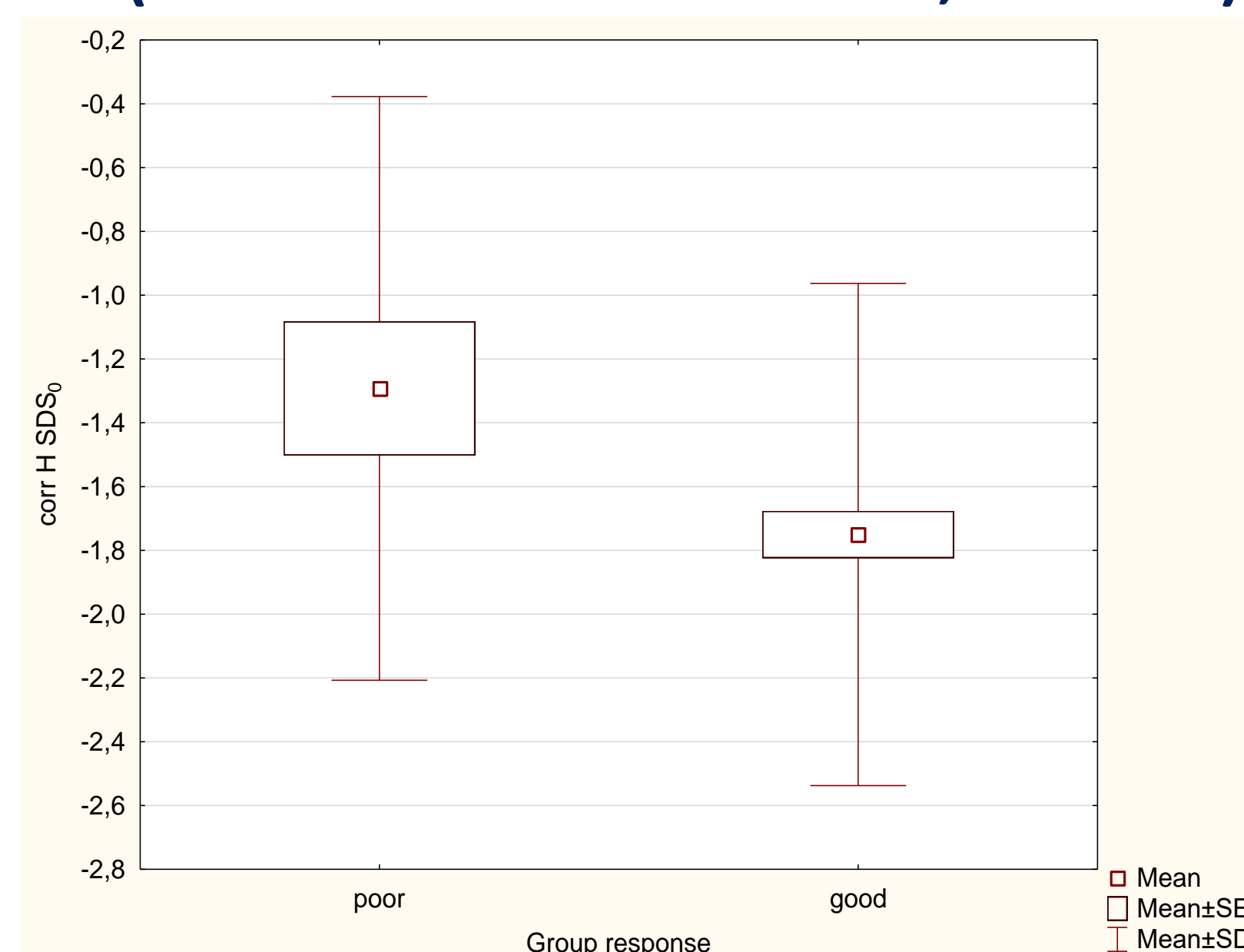
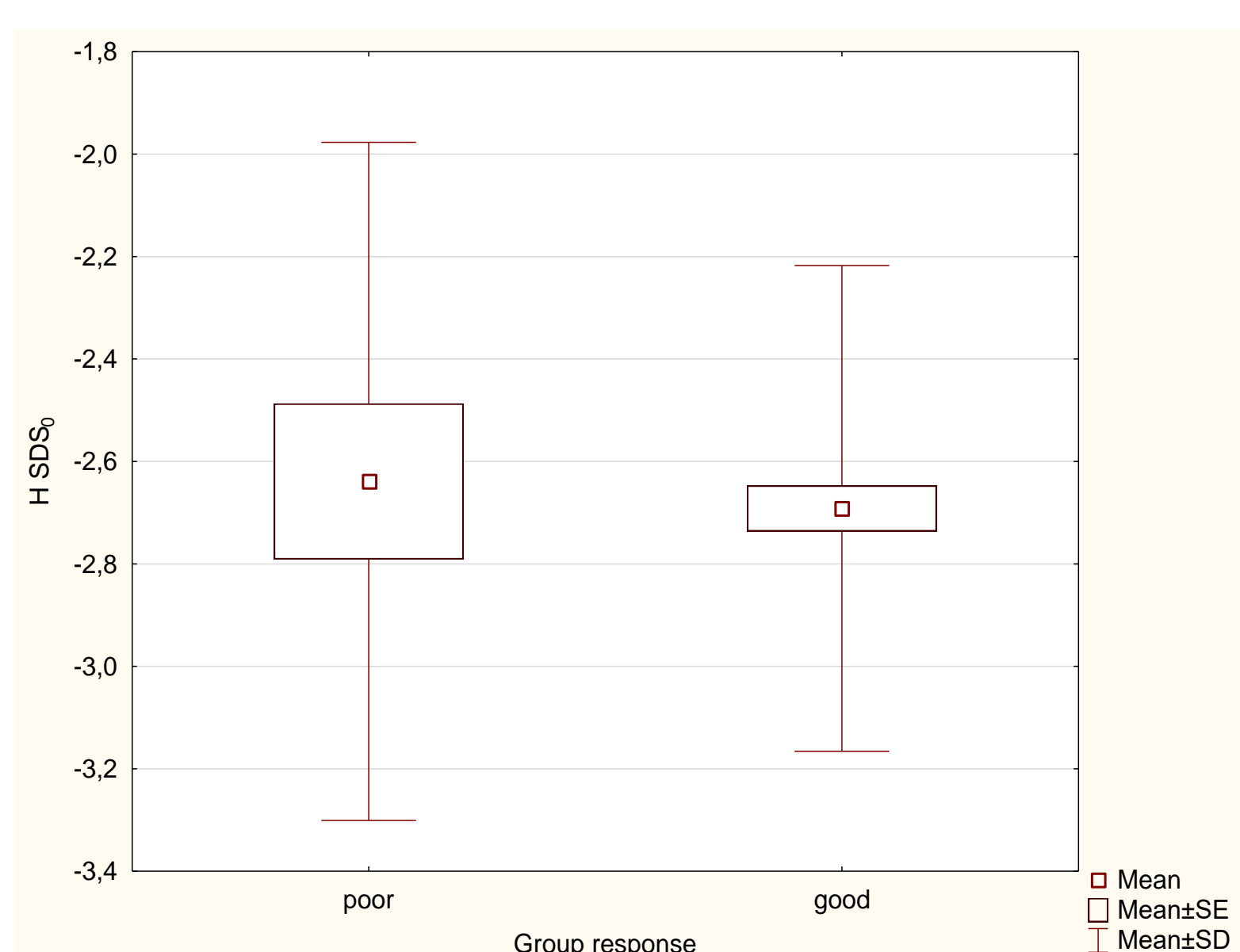


1. Patient's height SDS before treatment ($H\ SDS_0$)
2. Change of height SDS in pre-treatment period ($H\ SDS\ V_0$)
3. Patient's body mass SDS ($M\ SDS$)
4. Patient's chronological age (CA)
5. Bone age to chronological age ratio (BA/CA)
6. Gender (G)
7. Pubertal development (PUB):
 - 0 pre-pubertal
 - 1 pubertal
8. Mother's height SDS ($H_M\ SDS$)
9. Father's height SDS ($H_F\ SDS$)
10. IGF-I concentration (expressed as $IGF-I\ SDS$ for age and gender)
11. IGFBP-3 concentration expressed as ($IGFBP-3\ SDS$)
12. GH peak in test with clonidine (GH_K),
13. GH peak in test with glucagon (GH_G)
14. GH peak after falling asleep (GH_N)
15. Birth weight ($BW\ SDS$)
16. Gestational age (GA)
17. Initial rhGH dose (D)
18. Patient's height SDS increase during 1st year of treatment ($H\ SDS\ V_1$)
19. IGF-I SDS increase after 3-6 months of treatment ($\Delta\ IGF-I\ SDS$)
20. IGFBP-3 SDS increase at the same time point ($\Delta\ IGFBP-3\ SDS$).

see: Smyczyńska U et al.
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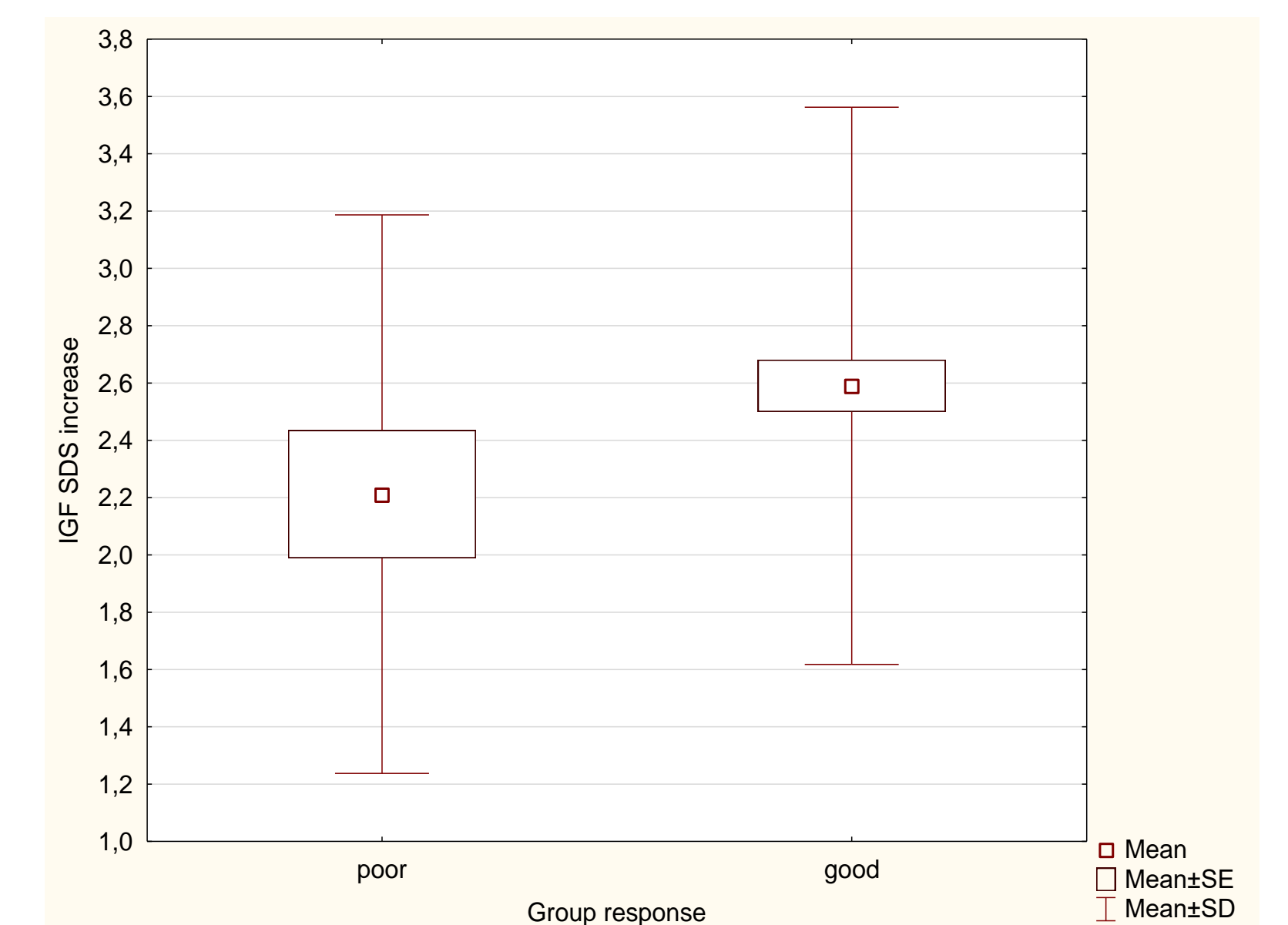
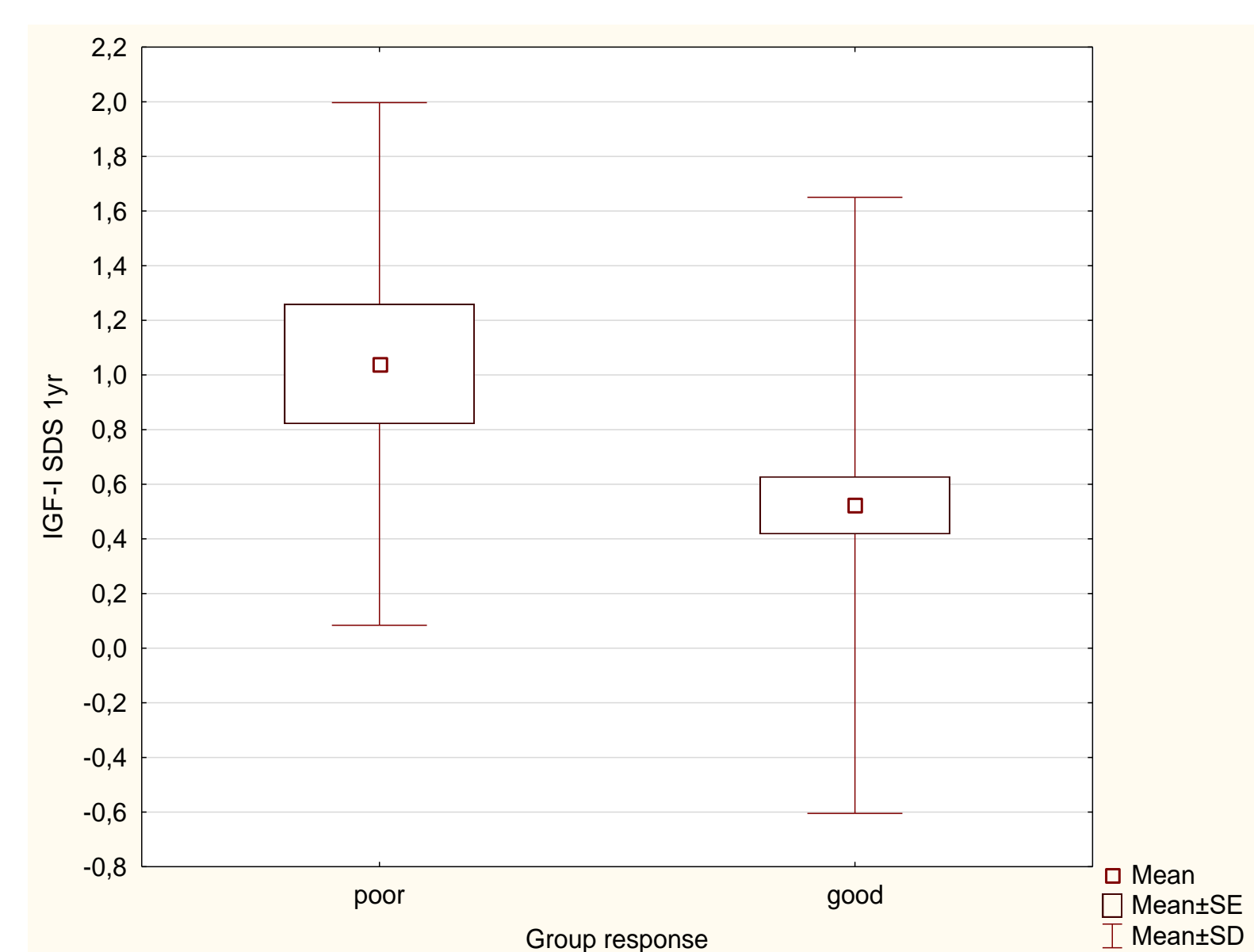
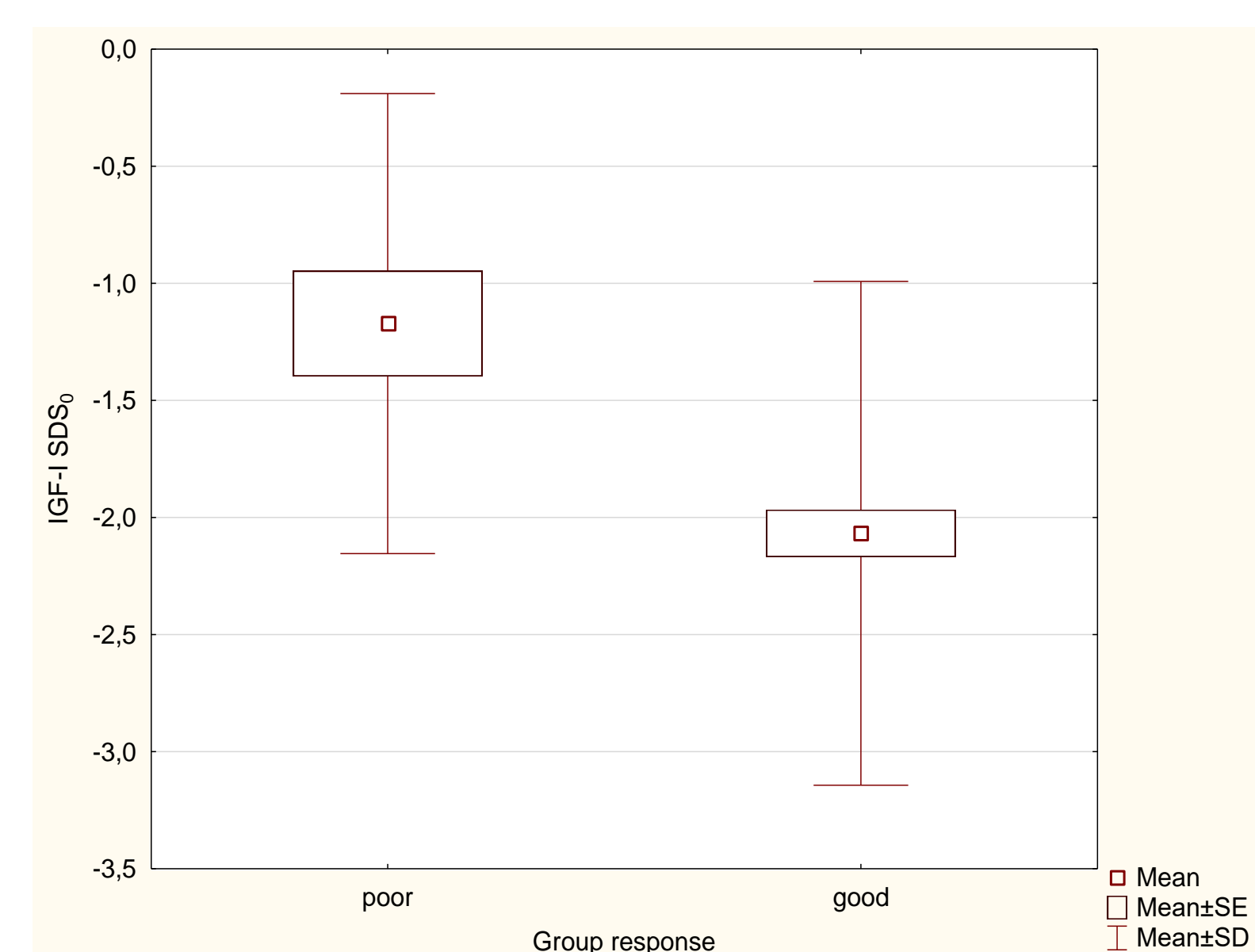
According to the increase of FH SDS with respect to $H\ SDS_0$ below or over 1.0 SD, the patients were classified as poor and good responders, respectively.

Both groups had similar $H\ SDS_0$ but in poor responders it was significantly higher than in good responders (-1.29 ± 0.79 vs. -1.75 ± 0.78 , $P=0.03$) while corrected by target height (TH) SDS (corr $H\ SDS_0$); pre-treatment growth rate ($H\ SDS\ V_0$) was significantly better in poor than in good responders (-0.09 ± 0.20 vs. -0.25 ± 0.21 , $P=0.002$).



Poor responders had insignificantly higher IGF-I SDS than good responders before treatment (-1.17 ± 0.96 vs. -2.07 ± 1.07 , $P=0.06$) and in 1st year of therapy (1.04 ± 0.93 vs. 0.52 ± 1.12), however IGF-I SDS increase was insignificantly lower in poor than in good responders (2.21 ± 0.95 vs. 2.59 ± 0.97).

There were no similar differences for IGFBP-3.



As all but one poor responders were GH-deficient, further comparison between GHD and ISS was performed only for good responders.

Among good responders, all the differences between GHD and ISS were insignificant, except for that in GH secretion (the detailed values for selected variables are presented in the Table).

| | GHD | ISS | P |
|----------------------------------|------------------|------------------|------|
| $H\ SDS_0$ | -2.64 ± 0.46 | -2.84 ± 0.50 | 0.06 |
| corr $H\ SDS$ | -1.74 ± 0.80 | -1.78 ± 0.74 | 0.61 |
| $H\ SDS\ V_0$ | -0.27 ± 0.21 | -0.20 ± 0.19 | 0.07 |
| IGF-I SDS_0 | -1.99 ± 1.07 | -2.29 ± 1.08 | 0.15 |
| IGF-I $SDS\ 1\ yr$ | 0.59 ± 1.16 | 0.33 ± 1.03 | 0.27 |
| IGF-I $SDS\ increase$ | 2.58 ± 0.96 | 2.62 ± 1.03 | 1.00 |
| FH SDS | -0.83 ± 0.60 | -0.97 ± 0.57 | 0.22 |
| FH $SDS\ increase\ vs\ H\ SDS_0$ | 1.81 ± 0.52 | 1.87 ± 0.56 | 0.67 |

More severe deficit of height with respect to TH, decrease of height SDS before treatment and more severe IGF-I deficiency were the main predictors of good response to GH therapy, with no difference between GHD and ISS.

In poor responders decreased IGF-I sensitivity should be taken into account.

Neural models are useful for identification of variables that should be subjected to further analysis.