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Prediction of Adult Height in Growth-Hormone-Treated Children with Growth Hormone Deficiency

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Context: Several studies have searched for factors that significantly influence adult height (AH) of children with GH deficiency (GHD) who have been treated with biosynthetic GH, but a prediction model for AH has not yet been presented.

Objective: Our objective was to develop models for prediction of AH, using information available at the start of GH treatment or after 1 yr of treatment.

Design and Setting: For this retrospective study, data were collected from the National Registry of Growth Hormone Treatment in Children, which contained data of Dutch children treated with GH.

Patients/Intervention: Patients included males born before 1985 and females born before 1987 with either diagnosis of GHD (syndromes, tumors, and other diseases were excluded) or a maximal GH response during provocation tests of less than 11 ng/ml, treated with biosynthetic GH for at least 1 yr. To be able to use the complete group of 342 children for the development of the models, multiple imputation was used for missing values.

Main Outcome Measure: We assessed AH SD scores (SDS).

Results: Each prediction model contained both target height SDS and current height SDS. The change in height SDS during the first year proved an important predictor for AH. In all models, addition of GH dose was not significant. The percent explained variance, after correction for overfitting, ranged from 37% (prepubertal children, prediction at start) to 60% (pubertal children, prediction after 1 yr).

Conclusion: The presented prediction models give accurate predictions of AH for children with GHD at start and after 1 yr of GH treatment. They are useful tools in the treatment of these children. (***J Clin Endocrinol Metab* 92: 925–931, 2007**)

TREATMENT WITH BIOSYNTHETIC GH is successful in improving adult height (AH) in children with GH deficiency (GHD). The reported mean AH SD scores (SDS) range from −1.6 to −0.7, and the mean change in height SDS during GH treatment ranges from 1.1–2.0 (1–6).

Several prediction models have been developed for short-term growth response to GH treatment in children with GHD (7–9). For example Ranke *et al.* (8) developed models for prepubertal children predicting height velocity (HV) (in centimeters per year) during the first, second, third, and fourth years of treatment. In the models predicting HV during the second year or later, the HV in the previous year was the most prominent predictor (7, 8). Cole *et al.* (10) analyzed first- and second-year growth response to GH treatment. They found that the maximal GH response during provocation tests was the most predictive factor for the first-year response, whereas the first-year response was much more important for the second-year response.

The following predictive factors for AH SDS were described: sex, birth weight SDS, age at start of GH treatment, height SDS at start for chronological age, height SDS at start for bone age (BA), weight SDS at start, target height (TH) SDS or midparental height SDS, maximal GH response during provocation tests, presence of multiple pituitary hormone deficiencies (MPHD), BA delay at start, pubertal stage at start, age at onset of puberty, height SDS at onset of puberty, HV in the first year of treatment, total GH dose, number of GH injections per week, duration of treatment, and completion of treatment until AH (1–4, 6, 11–14).

In three studies, a regression model was developed for AH SDS or change in height SDS during GH treatment in a group of children with GHD treated with biosynthetic GH (1, 2, 6). These studies, however, also included patient characteristics during long-term follow-up, for example height SDS at onset of puberty, duration of treatment, and mean GH dose during treatment.

Therefore, until now, an accurate model for the prediction of AH SDS at start or after 1 yr of GH treatment has not been developed.

In this study, we developed models for the prediction of AH SDS. We will first present a model using only information available at the start of the GH treatment and then second a model using information available after 1 yr of treatment, for prepubertal as well as pubertal children.

Patients and Methods

Patients

We used data from the National Registry of Growth Hormone Treatment in Children by the Dutch Growth Foundation, which contains data of more than 2200 Dutch children treated with GH. Registration started in 1992 and has been obligatory since 1997. We selected males born before 1985 and females born before 1987, to ensure a representative

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Abbreviations: AH, Adult height; BA, bone age; BMI, body mass index; GHD, GH deficiency; HV, height velocity; MPHD, multiple pituitary hormone deficiencies; SDS, SD scores; TH, target height.

group with AH. Other selection criteria used were diagnosis of GHD or a maximal GH response during provocation tests of less than 11 ng/ml and treatment with biosynthetic GH for at least 1 yr. Children with syndromes, tumors, or other diseases were excluded (Fig. 1).

For the development of the prediction models for application at the start of GH treatment, the group was divided into two subgroups, one including prepubertal children and one including pubertal children. For the models to be applied after 1 yr of GH treatment, the pubertal stage at that moment determined the prepubertal and pubertal subgroups.

Outcome and potential determinants

AH was defined as the height reached when growth velocity was less than 2 cm/yr and age above 14 yr. AH SDS was calculated using references for Dutch adults, *i.e.* a mean (SD) of 184.0 (7.1) cm for males and 170.6 (6.5) cm for females (15).

The potential determinants were as follows: 1) initial characteristics included sex, TH SDS, and birth weight SDS (16), 2) characteristics at start of GH treatment included age, height SDS, weight SDS (15), body mass index (BMI) SDS (17), BA and BA delay, maximal GH response during provocation tests, diagnosis (idiopathic GHD or GHD with abnormalities on pituitary magnetic resonance imaging), presence of MPHD, IGF-I SDS, and starting dose of GH; and 3) additional characteristics after 1 yr of treatment included height SDS and change in height SDS during the first year, weight SDS and change, BMI SDS and change, change in BA during the first year, and mean GH dose during the first year.

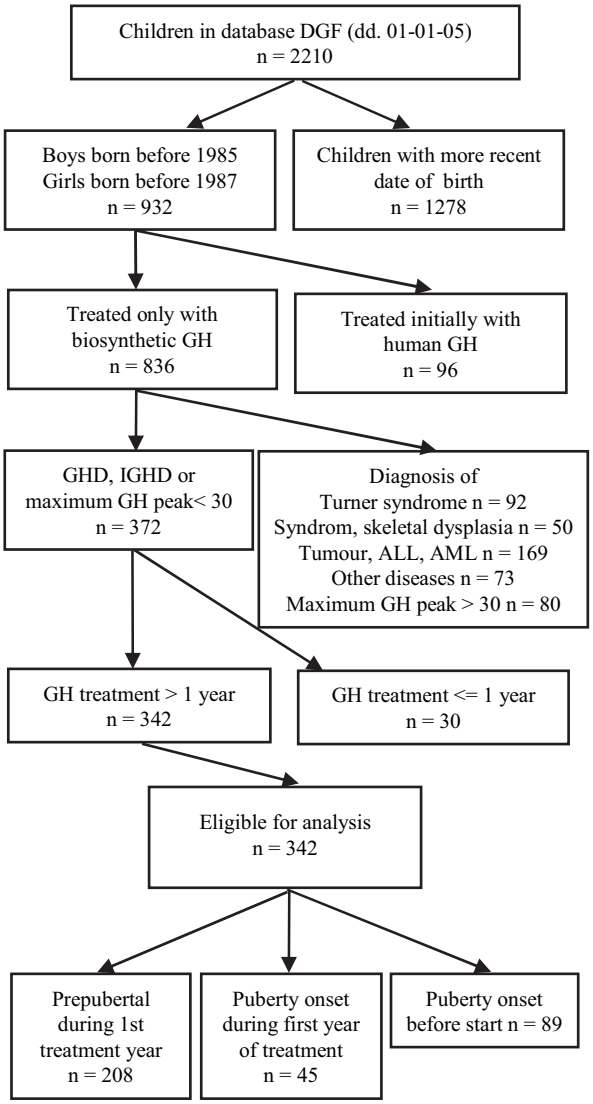

FIG. 1. Description of cohort.

First-year changes in height and weight SDS were corrected for the actual time between the two measurements (range, 0.7–1.3 yr).

Eighty-seven percent of the BA were determined according to Greulich and Pyle. When the BA was determined according to the Tanner-Whitehouse method or radius, ulna, short-bones score, it was converted to Greulich and Pyle estimations (18). BA delay was computed as chronological age minus BA. Bone maturation during the first year was computed as the ratio of the change in BA and the exact difference between the chronological ages at time of the BA measurements.

In 80% of patients, an arginine test was used to determine the maximal GH response, in 40% L-dopa, and in 24% clonidine. Eighty-two percent of children had GHD defined as a failure to increase serum GH levels above 11 ng/ml in two or more tests, whereas 18% had only one test.

Eighty percent of the IGF-I measurements were centrally performed in a laboratory with published reference values (19). For the remaining 20%, the laboratory-specific reference values for IGF-I were used to calculate the SDS. IGF-I measurements after 1 yr of treatment were not used, because these were very scarce (11%).

Multiple imputation

It is unavoidable that in a registry database some data are missing for some patients. For example, birth data and the height of parents can be missing for adopted children, and BA data are not complete because these measurements were not always performed in former years. Using only cases with complete data for all the potential determinants would result in a sample much smaller and likely not a representative group of the population.

To develop the prediction models on the complete group, we used multiple imputation for missing values in the outcome or in the potential determinants (20, 21). For each missing variable, a value was imputed, using the relations between the variables in the data set. Because an imputed value does not have the same accuracy as an observed value, the imputation procedure was executed five times to generate five completed data sets. In each data set, a different value was imputed, thus reflecting the uncertainty of the imputed value. For the multiple imputation, we used the procedure SAS Proc MI (22), which assumes that the variables have a multivariate normal distribution. Variables with a non-normal distribution were transformed to normality during the imputation procedure.

Each step in the data analyses was performed on each imputed data set separately, and the results were combined (20, 21).

Truncation of extreme values of potential determinants and outcome

Extreme values of the outcome or determinants can highly influence the estimation of regression coefficients in a model. To avoid this, the 1% lowest values of all continuous determinants were truncated to the first percentile and the 1% highest values to the 99th percentile.

Development of prediction model

For the development of the prediction model, we used forward selection with an inclusion criterion of $P = 0.05$. After the selection of the predictor variables, for each continuous predictor, it was tested whether adding the quadratic term or another transformation of the variable improved the model significantly (23).

We tested possible interactions of age or BA at start with TH SDS and with change in height SDS during first year if both main terms were selected in the model.

A possible relation between the predicted outcomes and the residuals was examined by evaluation of the scatter plots and by fitting the linear regression with the absolute value of the residuals as determinant and the predictions as outcome.

Internal validation

It is well known that a prediction model suffers from over-optimism (24, 25). The predictive performance of a prediction model in other data

sets than the set on which it is developed will be lower. The predicted values generated by the model will tend to be too extreme.

To remove the over-optimism of the derived model, we used bootstrap techniques (24, 26), shortly explained as follows. From the data set used for the development of a prediction model, a random sample was drawn, representing another but comparable data set. This sampling was done with replacement, so each subject could be selected several times, and consisted of the same number of subjects as the original data set. On this data set, called a bootstrap sample, a prediction model was developed, using the same procedure as for the development of the model in the original data set. The predictive performance of this model developed in the bootstrap sample was evaluated by calculating R^2, which gives the percentage of variance explained by the model, and by calculating the mean of the squared residuals. This evaluation was done in both the bootstrap sample and the original data set. The predictive performance is always better in the bootstrap sample, on which this model is developed, than in the original data set (higher R^2 and smaller residuals). The difference between these predictive performances is called the optimism. We generated 200 bootstrap samples and used the average optimism to correct the predictive performance of the original model (26). Furthermore, a linear regression was performed in each bootstrap sample with the observed values as outcome and the predicted values as determinant. The coefficient for the slope will usually be below one. This procedure is the same as for the validation of a model on external data (25). The mean of the 200 slopes was used as shrinkage factor for the estimated regression coefficients in the original derived prediction model. The intercept was adjusted to get the same mean predicted value (27). This resulted in a calibrated model that provides predictions less extreme than the predictions from the original model. The predictions calculated with the calibrated model will be accurate in new patients with GHD.

Results

The study group consisted of 342 children, of whom 208 were prepubertal for at least 1 yr after the start of GH treatment, and 89 were pubertal at the start of treatment. In 45 children, puberty started during the first year of treatment. Table 1 shows the characteristics of the study group and for each variable the percentage of patients with a missing value.

Prediction models at start of GH treatment

For the prediction of AH SDS using the characteristics available at the start of treatment (start model), the final model for prepubertal patients included six variables. Predictors with a positive effect were height SDS at start, TH SDS, female gender, and presence of MPHD, whereas maximal GH response during provocation tests and BA at start had a negative effect. The relation between height SDS at start and AH SDS (corrected for the other predictors) was quadratic. Starting dose of GH was not a significant predictor. In Table 2, the estimated coefficients of the model are given. The percent explained variance ($R^2 \times 100\%$) of the derived model was 43%. The optimism estimated by bootstrapping was 6%, so the corrected percentage is 37%. Corrected for optimism, the residual SD was 0.84. The estimated shrinkage factor for the correction of the regression coefficients was 0.94. The final prediction formula is given in Table 2.

For patients already pubertal at start, age at onset of puberty is also a potential determinant. For boys, we reduced

TABLE 1. Characteristics of the study group

	Prepubertal, at start and during first year of treatment (n = 208)	Start of puberty		Percentage with missing value
		During first year of treatment (n = 45)	Before start of treatment (n = 89)	
Male (%)	60	44	45	0
Birth weight SDS	−0.73 ± 1.31	−0.80 ± 1.13	−0.54 ± 1.37	14
TH SDS	−0.97 ± 0.96	−1.22 ± 0.91	−0.90 ± 0.87	5
At start				
Age (yr)	9.0 ± 3.3	12.8 ± 1.9	14.0 ± 2.0	0
Maximal GH peak (ng/ml)	4.5 ± 2.9	5.7 ± 3.0	5.2 ± 2.8	6
IGF-I SDS	−3.67 ± 2.76	−3.54 ± 3.44	−2.93 ± 3.18	37
Idiopathic GHD (%)	83	99	88	0
Presence of MPHD (%)	41	24	30	0
Height SDS	−3.40 ± 1.01	−3.32 ± 0.97	−2.92 ± 1.14	0
Weight SDS	−2.54 ± 1.48	−2.01 ± 1.44	−1.79 ± 1.68	0.3
BMI SDS	−0.35 ± 1.21	−0.06 ± 1.20	−0.10 ± 1.36	0.3
BA (yr)	6.5 ± 3.0	10.4 ± 2.0	12.0 ± 1.6	11
BA delay (yr)	2.6 ± 1.5	2.4 ± 1.3	2.0 ± 1.5	11
GH dose (mg/m^2·d)	0.71 ± 0.24	0.72 ± 0.26	0.73 ± 0.26	1
After first year				
Height SDS	−2.69 ± 0.95	−2.88 ± 1.05	−2.34 ± 1.13	0
Weight SDS	−2.08 ± 1.39	−1.74 ± 1.51	−1.44 ± 1.59	0.3
BMI SDS	−0.51 ± 1.24	−0.12 ± 1.28	−0.08 ± 1.34	0.3
Change in height SDS	0.71 ± 0.51	0.44 ± 0.36	0.58 ± 0.38	0
Change in weight SDS	0.45 ± 0.51	0.27 ± 0.49	0.35 ± 0.47	0.3
Change in BMI SDS	−0.17 ± 0.57	−0.06 ± 0.49	0.01 ± 0.46	0.3
Mean GH dose (mg/m^2·d)	0.71 ± 0.23	0.75 ± 0.27	0.75 ± 0.27	0.6
Adult height				
Duration GH treatment (yr)	7.9 ± 3.3	3.9 ± 1.3	3.3 ± 1.2	4
Mean GH dose (mg/m^2·d)	0.77 ± 0.21	0.80 ± 0.27	0.80 ± 0.24	8
AH SDS	−1.71 ± 0.91	−2.02 ± 1.08	−1.68 ± 0.94	20
Change in height SDS	1.72 ± 1.10	1.36 ± 0.81	1.18 ± 1.16	20
AH SDS − TH SDS	−0.74 ± 1.04	−0.68 ± 0.75	−0.85 ± 0.88	22

Results are expressed as mean ± SD or percentage.

TABLE 2. Results of the final models for prediction of AH at start of treatment (start model)

Predictor variable	Prepubertal (n = 253)				Pubertal (n = 89)			
	Estimated coefficient	SE	*P*	Partial r^2	Estimated coefficient	SE	*P*	Partial r^2
Intercept	1.399	0.502	0.006		−0.645	0.226	0.006	
Height SDS at start	1.092	0.260	<0.0001	0.239	0.456	0.080	<0.0001	0.281
(Height SDS at start)^2	0.082	0.035	0.02					
TH SDS	0.282	0.060	<0.0001	0.086	0.428	0.100	<0.0001	0.188
Maximal GH peak (ng/ml; ln)	−0.158	0.064	0.02	0.022				
Gender (0 = male, 1 = female)	0.278	0.108	0.01	0.022				
MPHD (0 = no, 1 = yes)	0.323	0.124	0.01	0.023				
BA at start (yr)	−0.051	0.017	0.003	0.031				
BA delay at start (yr)					0.265	0.058	<0.0001	0.213
R^2 corrected for optimism (original)	0.37 (0.43)				0.41 (0.53)			
Residual SD corrected (original)	0.84 (0.79)				0.83[a] (0.72[b])			
Shrinkage factor	0.94				0.91			

Prediction formulas after bootstrap correction are as follows: for the prepubertal group, AH SDS = 1.186 + 1.021 × H SDS_{start} + 0.077 × H SDS_{start}^2 + 0.264 × TH SDS − 0.148 × ln(max GH) + 0.260 × gender + 0.302 × MPHD − 0.047 × BA; for the pubertal group, AH SDS = −0.746 + 0.416 × H SDS_{start} + 0.391 × TH SDS + 0.242 × BA delay. ln, Natural log.

[a] Accounting for the relation with the predicted value: corrected residual SD = $\sqrt{[(0.38 - 0.19 \times \text{predicted value})^2 + 0.17]}$.

[b] Accounting for the relation with the predicted value: original residual SD = 0.38 −0.19 × predicted value.

the age at onset by 0.8 yr, according to the difference in mean age at onset of puberty between boys and girls in the Dutch population, as found by Fredriks *et al.* (15). For this group, the start model included three variables, height SDS at start, TH SDS, and BA delay at start, all with positive effect (Table 2). Again, starting dose of GH was not in the final model. The percent explained variance was 53% and after correction for optimism, 41%. For this prediction model, there was a significant relation between the predicted values and the residual SD. The residual SD was decreasing with increasing predicted value, according to the equation residual SD = 0.38 − 0.19 × predicted value. This residual SD has to be adjusted using the optimism estimated by bootstrapping (see note at Table 2). The estimated shrinkage factor for the correction of the regression coefficients was 0.91.

Prediction models after 1 yr of treatment

Using the characteristics available after 1 yr of treatment (first-year model), the prediction model for prepubertal patients included height SDS after the first year (quadratic relation), TH SDS, female gender, presence of MPHD, BA delay at start, and change in height SDS during the first year, all with a positive effect. The estimated coefficients are given in Table 3. As in the start model, addition of starting dose of GH was not significant, nor was mean GH dose during the first year. If the latter was added to the final model, its influence on AH SDS was negative, the estimated coefficient being −0.35 ($P = 0.11$), whereas the coefficients of the other predictors did not change substantially (all changes < 10%). The percent explained variance of the final model was 51% and, after correction for optimism, 43%. The residual SD after correction for optimism was 0.76. The estimated shrinkage factor for the correction of the regression coefficients was 0.94.

The predictors in the first-year model for children who are pubertal after 1 yr of GH treatment were height SDS after the first year, TH SDS, BA delay at start, and change in height SDS during the first year. The mean GH dose during the first year was not a significant predictor. The explained variance was 66% and after bootstrapping was reduced to 60%. Corrected for optimism, the residual SD was 0.69. The estimated shrinkage factor for the correction of the regression coefficients was 0.95.

In Table 4 and Fig. 2, examples are given of the use of the

TABLE 3. Results of the final models for prediction of AH after 1 yr of GH treatment (first-year model)

Predictor variable	Prepubertal (n = 208)				Pubertal (n = 134)			
	Estimated coefficient	SE	*P*	Partial r^2	Estimated coefficient	SE	*P*	Partial r^2
Intercept	0.075	0.330	0.82		−0.866	0.189	<0.0001	
Height SDS after first year	1.250	0.213	<0.0001	0.336	0.527	0.064	<0.0001	0.385
(Height SDS after first year)^2	0.114	0.035	0.001					
TH SDS	0.200	0.057	0.0006	0.065	0.347	0.074	<0.0001	0.162
Gender (0 = male, 1 = female)	0.348	0.106	0.001	0.054				
MPHD (0 = no, 1 = yes)	0.309	0.107	0.004	0.043				
BA delay at start (yr)	0.100	0.038	0.008	0.039	0.164	0.044	0.0003	0.103
Change in height SDS in first year	0.308	0.105	0.004	0.044	0.500	0.163	0.003	0.070
R^2 corrected for optimism (original)	0.43 (0.51)				0.60 (0.66)			
Residual SD corrected (original)	0.76 (0.69)				0.69 (0.62)			
Shrinkage factor	0.94				0.95			

Prediction formulas after bootstrap correction are as follows: for the prepubertal group, AH SDS = −0.049 + 1.169 × H SDS_{1yr} + 0.107 × H SDS_{1yr}^2 + 0.187 × TH SDS + 0.325 × gender + 0.289 × MPHD + 0.094 × BA $delay_{start}$ + 0.288 × ΔH SDS_{1yr}; for the pubertal group, AH SDS = −0.915 + 0.502 × H SDS_{1yr} + 0.331 × TH SDS + 0.156 × BA delay + 0.477 × ΔH SDS_{1yr}.

TABLE 4. Examples of predictions for prepubertal children

	Child 1	Child 2
Characteristics		
Height SDS at start	−3.0	−4.0
TH SDS	−1.0	−2.0
Maximal GH peak (ng/ml)	2.0	7.0
Gender	Girl	Boy
MPHD	Yes	No
BA at start (yr)	6.0	8.0
BA delay at start (yr)	2.6	0.0
Height SDS after first year	−2.2	−3.3
Change in height SDS in first year	0.8	0.7
Predictions (95% prediction interval)		
Without any model	−1.77 (−3.61 to 0.07)	−1.77 (−3.61 to 0.07)
Start model	−1.27 (−2.92 to 0.38)	−2.86 (−4.50 to −1.21)
First-year model	−1.20 (−2.69 to 0.28)	−2.92 (−4.41 to −1.43)

The prediction intervals are calculated using the relevant SD, *i.e.* 0.94 without model, 0.84 for the start model, and 0.76 for the first-year model. Example of calculation, child 1, start model, follows: predicted AHSDS = $1.186 + 1.021 \times (-3) + 0.077 \times (-3)^2 + 0.264 \times (-1) - 0.148 \times \ln(2) + 0.260 \times 1 + 0.302 \times 1 - 0.047 \times 6 = -1.27$. ln, Natural log.

prediction models for prepubertal children. Without any model, we would predict the AH SDS of each individual prepubertal child with GHD and GH treatment as −1.77 (being the mean AH SDS of the children prepubertal at start) with a 95% prediction interval of −3.61 to 0.07. Table 4 gives the characteristics and the predictions of a (hypothetical) child with relatively positive prospects (child 1) and a child with less favorable characteristics (child 2). In Fig. 2, the distributions of the predictions with the first-year model are plotted for the children in this example. For child 1, the predicted probability of reaching an AH SDS above −2 is 85%, and for child 2, this is only 11%.

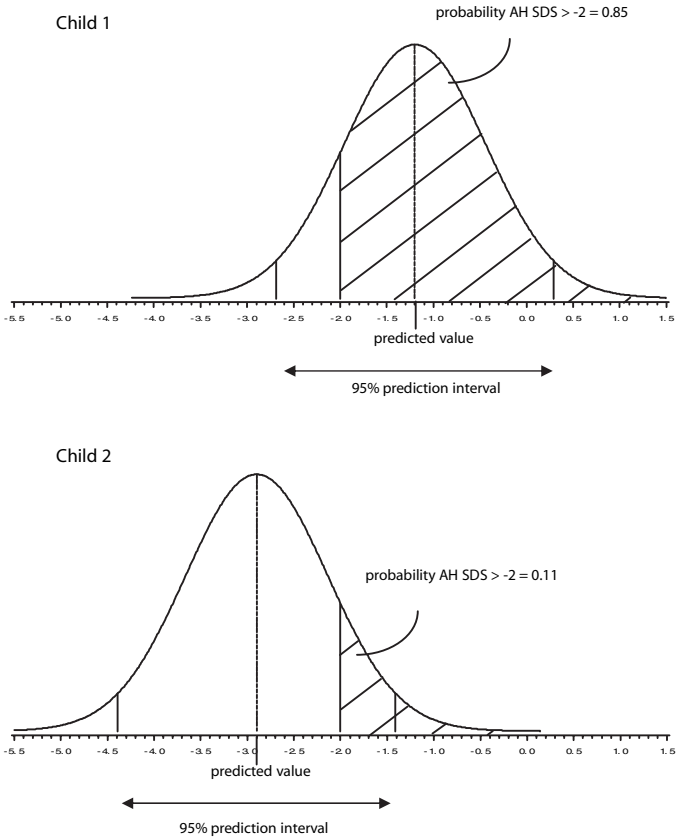

FIG. 2. Examples of the distribution of the predicted value for AH SDS after 1 yr of treatment. For the characteristics of the children used in these examples, see text.

Discussion

In the present study, we have developed prediction models for AH SDS for prepubertal and pubertal children with GHD treated with GH, according to state-of-the-art statistical methods. This includes dealing with missing data, investigation of more flexible relations between continuous determinants and the outcome, and correction for over-optimism (24).

A prediction model for AH SDS is a useful tool for the clinician to become informed about the prospective long-term results of GH treatment. A prediction is desired before the start of treatment. Application of the prediction model gives a patient his or her individual predicted value with prediction interval. It can identify patients with high or low chance of benefit from GH treatment. After 1 yr of treatment, the expectations can be refined, which is useful for decisions about the continuation of GH treatment.

The prediction models presented in this paper explain percentages of variance in AH SDS from 37% (prepubertal group, start model) to 60% (pubertal group, first-year model). The outcome is usually several years ahead from the moment of prediction. During childhood, many factors may influence the growth of a child, so we could expect that a substantial part of the variance remains unexplained.

As expected, all models show height SDS (at start or after 1 yr of GH treatment) and TH SDS as most important predictive factors. A positive effect of female gender was found, in line with Carel *et al.* (1). They attributed this to sex-dependent differences in pubertal age. It is also possible that girls have a better compliance than boys. Children with MPHD had a more favorable outcome compared with children with isolated GHD, as previously reported by Reiter *et al.* (6). The negative coefficient for BA in the model for prepubertal children reflects that the start of GH treatment at a younger age gives a higher growth response. It appeared that BA is a more informative predictor than chronological age. The positive coefficients for BA delay in the other models

reflect that children with delayed BA have more growth potential.

Maximal response to GH provocation tests is included in the start model for prepubertal children (negative effect) but is not significant anymore in the first-year model. A similar finding was reported by Cole *et al.* (10). The first-year models include change in height SDS during the first year, which is in line with several other studies (2, 3, 6, 11).

In none of the models was GH dose selected as a significant predictor variable. Notably, this has also been reported by others (1, 6). For clinical practice, it might have been desirable if the prediction models could lend support in finding the optimal GH dose. A practical and logical question is what would be the predicted AH SDS if a higher or lower dose than the standard dose is prescribed? A significant positive effect of GH dose on short-term growth response is often found (8, 28, 29), but the dose effect on the long-term response is less established (3, 6, 30). For the patients in our data set, the GH dose at the start and during treatment was assessed by the clinician based on unknown criteria. In 80% of the patients, the mean GH dose during treatment was in the range of 0.5–1.0 mg/m^2·d (median, 0.72 mg/m^2·d). It is possible that higher initial doses were prescribed to patients with supposed worse prospects, like children close to or entering puberty, children with only mild GHD, or children with very small parents. During treatment, a change of GH dose might have been guided by the obtained growth response. Our data are therefore not suitable to estimate the effect of GH dose on AH SDS. This would only be possible if the dosages given were randomly assigned and had remained unchanged during treatment, as in randomized controlled trials.

One of the arguments for developing the first-year models was to investigate whether such a model could provide a criterion for the first-year growth response needed for an AH in the desired (normal) range. Indeed, our study shows that change in height SDS during the first year of treatment is highly related to the AH attainment. Because a positive correlation between GH dose and first-year response is well established, one might tend to give a high GH dose to increase the first-year response, with the idea that this will subsequently increase AH. However, we found an inverse relation between first-year GH dose and AH, although this did not reach significance. This means that a first-year growth response obtained by a high GH dose gives a lower predicted AH than the same response obtained by a low GH dose.

We performed internal validation of the prediction models by bootstrapping. This results in models corrected for overfitting. It is not necessary to validate or calibrate the models with an external validation. Applying the models to data of an independent cohort is still interesting. In conclusion, the prediction models presented in this study can be a useful tool for decisions about GH treatment of children with GHD.

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