

## Prediction of Adult Height Based on Automated Determination of Bone Age

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**Context:** Adult height prediction is a common procedure in pediatric endocrinology, but it is associated with a considerable variability and bias from the bone age rating.

**Objective:** A new method for adult height prediction is presented, based on automated bone age determination.

**Method:** The method predicts the fraction of height left to grow from age and BoneXpert bone age. This is refined by drawing the prediction toward the population mean, or alternatively toward the height predicted from the parents' heights. Boys' body mass index and girls' height at menarche can be included optionally as predictors.

**Participants:** A total of 231 normal children from the First Zurich Longitudinal Study (1ZLS) were followed from age 5 until cessation of growth with annual x-rays of the left hand. A total of 198 normal children from the Third Zurich Longitudinal Study were used for validation.

**Results:** The root mean square error of adult height prediction (Tanner-Whitehouse 3 method in parentheses considered as standard for accuracy) on the 1ZLS was 3.3 cm (3.5 cm) for boys aged 10–15 yr and 2.7 cm (3.1 cm;  $P < 0.005$  for difference to Tanner-Whitehouse 3) for girls aged 8–13 yr. High body mass index before puberty negatively affected adult height of boys, independent of bone age.

**Conclusions:** With the new method, adult height prediction has become objective because the dependence on manual bone age rating is eliminated. The method is well-suited to analyze large studies and provide a consistent body of evidence regarding the relation between maturation, body mass, and growth across populations, conditions, and ethnicities. (*J Clin Endocrinol Metab* 94: 4868–4874, 2009)

The prediction of a child's adult height is a common procedure in pediatric endocrinology. It is performed, for example, in children who are exceptionally short or tall relative to their age. The first model to predict adult height based on bone age (BA) was presented by Bayley in 1946 (1), and she adapted it with Pinneau in 1952 (2) to the Greulich-Pyle BA atlas (3). Since then, several alternative methods have appeared, notably, the Tanner-Whitehouse (TW) methods mark I (4), mark II (5), and TW3 (6) and the Roche-Wainer-Thissen (RWT)

method (7). These methods have a common shortcoming in that they are all based on manual BA determination, which is susceptible to considerable rater variability. This variability contributes to the SD of the prediction error, and a systematic difference (a bias) between raters leads to a bias in the predictions. This vulnerability of height predictions has made it difficult to validate and compare the various height prediction models, and only one previous study included a computerized BA method (8). Whenever a bias was observed, one could not disentangle the effects

of the studied population, the prediction method *per se*, and a possible bias in the BA rating. Other problems with existing methods include uncertainty regarding their validity for children of short or tall stature, or of advanced or retarded BA. In addition, there is a need for a more rational approach to incorporating knowledge concerning parents' heights, body weight, and age at menarche.

The aim of this work is to present a new method for height prediction based on automatic BA determination (9–12). The method is intended only for normal children and untreated children who can be considered extreme variations of normal children. It is not intended for children with pathology such as Turner syndrome or GH deficiency.<sup>1</sup>

## Subjects and Methods

### The modular principle of the new method

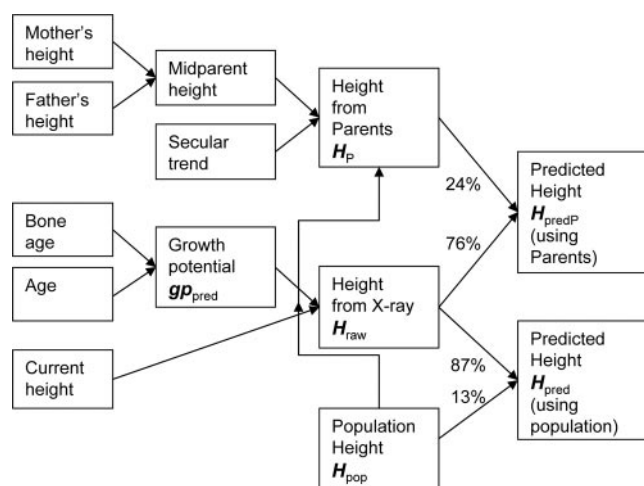
Existing methods of adult height prediction (6, 7) typically use a regression model where the explanatory variables, BA, chronological age (CA), current height, and sometimes weight and midparental height, are combined in one formula. This leads to a “black box” model, which is difficult to understand and difficult to extend to new populations without reestimating the entire model *de novo*. The new method is divided into simple, intuitively clear modules shown in Fig. 1, and the final prediction is based on combining the individual modules. After presenting the data material, we build up the framework module by module and explain how the pieces are integrated.

### Subjects: First Zurich Longitudinal Study (1ZLS)

The model is based on data from the 1ZLS of growth (13). These children were born between 1954 and 1956, and 231 of these (119 boys and 112 girls) were followed from birth to adulthood with careful annual height measurements and hand x-rays, which are preserved from approximately 5 yr and up. The x-rays have recently been digitized and processed with the BoneXpert automated BA method (Visiana, Holte, Denmark; www.boneXpert.com) (14), which is commercially available as a medical device in Europe and has the status of an investigational device in the United States. In this study, only the left hand x-rays were used. From 8 to 18 yr, 95% of the subjects have an automated BA value, whereas at 7, 6, and 5 yr the percentages drop to 90, 75, and 50%, respectively, because the older images tended to deteriorate. The adult height of all children was defined as the height when growth was less than 0.5 cm during the last 2 yr. The heights of the parents were measured for 95% of the children when the children were 5 yr old. A skinfold measure was formed as the average of the four skinfold measurements (biceps, triceps, subscapular, and suprailiac).

The mean (SD) of the parents' heights was 173.2 (6.8) cm for the fathers and 162.0 (6.2) cm for the mothers. The adult height of the children was 178.2 (7.0) cm for the boys and 165.0 (5.9) cm for the girls. Thus, the secular trend was 5 cm for males and 3 cm for females.

The model was validated on the Third Zurich Longitudinal Study (3ZLS) of growth and development, which included children having



**FIG. 1.** The information flow in the new method for adult height prediction. The weights at the arrows are approximate values for prepubertal children; the exact weights depend on BA and are listed in Supplemental Tables 4 and 5. The corrections for BMI and height at menarche are not shown. A calculator is available at <http://www.bonexpert.com/index.php/adult-height-predictor>.

one parent in the 1ZLS. Most of these children had x-rays at ages 7, 10, 12, 14, 16, and 18 yr. Children with a height measurement at age 18 yr were included. A boy with BA 13.6 yr at age 18 was excluded, resulting in 98 boys and 100 girls born between 1973 and 1991.

Informed consent was obtained from participants and parents. The ethics committee of the University Children's Hospital Zurich confirmed that the studies were performed according to the Declaration of Helsinki and conformed to legal and ethical norms.

### Bayley-Pinneau's scaling law

Bayley (1) took a particularly simple starting point for the prediction of adult height. She assumed that two normal children of the same age and BA, but of different height, have the same *fraction* left to grow. This is based on the notion that biology does not change if everything is scaled up by a small factor (for example, 1.2), and she found that this “scaling law” led to a good description of the data. It is an example of economy of explanation—experience from a group of children in one height range can be transferred to children in another height-range—*i.e.* it serves as a vehicle for generalizing our knowledge.

From the adult height  $H$  and the current height  $h$ , we define the growth potential as:  $gp = (H - h)/H$ . Bayley-Pinneau's scaling law then states that the growth potential can be predicted, to a good approximation, as a function solely of BA and CA – BA. This prediction is denoted  $gp_{pred}(BA, CA - BA)$ , or simply  $gp_{pred}$ , and from this expression, we form the so-called *raw* prediction of the adult height:  $H_{raw} = h/(1 - gp_{pred})$ . We call it “raw” because it will be refined in the new method, whereas the Bayley-Pinneau method used  $H_{raw}$  as the final prediction. In the Bayley-Pinneau method, the  $gp_{pred}(BA, CA - BA)$  function was estimated for continuous values of BA, but not for all values of the difference CA – BA. It is quoted only for the three ranges: advanced BA, BA > CA + 1 yr; normal BA, CA – BA < 1 yr; and retarded BA, BA < CA – 1 yr. This is a cruder representation than desired, but their work was conceived before computers were available.

<sup>1</sup> To work for such children, the model would need more parameters, *e.g.* the “severity” of the pathology and the GH dose.

The new method constructs  $gp_{pred}$  (BA, CA – BA) as a non-linear function of two variables. This is implemented as one neural network (a standard nonlinear regression method) for each gender as described in the Supplemental Material (Appendix A), published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>.

### Prediction of adult height from parents' heights

As part of the new height prediction method, we need a model that predicts the adult height of a child solely from the parents' heights.

This prediction is based on the midparental height:

$$H_{mid} = \frac{1}{2} (H_{mother} + H_{father})$$

This prediction of  $H$  is denoted as  $H_p$  (P for “parents”) and has the form:  $H_p = a H_{mid} + b + sec$ . Here  $a$  and  $b$  are estimated from the data with separate formulae for boys and girls, and the secular trend,  $sec$ , is separated from the constant term, so that the model can be estimated on the 1ZLS and then generalized to populations with a different secular trend. Several studies have shown that the secular trend today is smaller than the 4 cm observed in 1ZLS (15). This prediction model goes back to Galton (1859), who found that  $a$  is less than 1 and named this phenomenon “regression toward mediocrity” (16). Children of extraordinary parents are, on average, less extraordinary than their parents, *i.e.* they regress toward the average of the general population. To avoid a bias when the model is applied to populations with a different mean,  $H_{pop}$ , we add a term that removes the expected bias, so the final model is

$$H_p = aH_{mid} + b + (1-a)(H_{pop} - H_{pop1ZLS}) + sec$$

where  $H_{pop1ZLS}$  is 178.2 cm for boys and 165 cm for girls.

### The final adult height prediction

In the previous sections we have presented the two sources of information on adult height:

- **Relative height model:** The Bayley-Pinneau type prediction.  $H_{raw} = h/(1 - gp_{pred})$  which makes predictions relative to the current height.
- **Absolute height models**, so named because they make predictions in absolute terms. Here there are two options: 1) knowledge of height inferred from the parents' heights, expressed as the prediction  $H_p$ ; and 2) knowledge of height inferred from the population. This may, at first, appear as a poor model; however, as we shall see, it is very useful in combination with the relative height model. This prediction is called  $H_{pop}$  and it is 178.2 cm for boys and 165 cm for girls, in the case of the 1ZLS.

The new method arrives at the final prediction by combining the *relative* model prediction with one of the *absolute* model predictions. This is achieved by using a weighted average where the weights are determined from the relative uncertainties of the two pieces of knowledge. The theoretical background for this combination is Bayesian inference (17), as illustrated by the following example (more details are provided in Appendix B). If we have

two predictions of the adult height with independent prediction errors, one with SD of 3 cm and the other with SD of 6 cm, then one defines the (Bayesian) precisions of these predictions as  $1/SD^2$ , *i.e.* the precisions have the ratio 4:1. The optimal combination of the two predictions is the average, weighted with these precisions (*i.e.* the more imprecise prediction enters with a weight of 20%). Thus, if we have knowledge of the parents' heights, the final prediction of adult height,  $H_{predP}$ , is:  $H_{predP} = (1 - w_p) H_{raw} + w_p H_p$ . The weight,  $w_p$ , depends on BA, but is approximately 24% before puberty. This formula “draws” the raw Bayley-Pinneau-type prediction 24% of the way toward the prediction  $H_p$ . Likewise, if we choose not to use the parents' heights, we must invoke the population mean, and the final prediction of adult height becomes:  $H_{pred} = (1 - w_{pop}) H_{raw} + w_{pop} H_{pop}$ . Again,  $w_{pop}$  is a function of BA and is approximately 13% before puberty, *i.e.* the raw prediction is drawn 13% of the way toward the population mean.

### Adjustment for weight

An adjustment for the weight of the child is an optional module that relates the SD score (SDS) of the body mass index (BMI) to a correction of the adult height prediction.

### Menarche

The TW method for height prediction incorporated knowledge about menarche by constructing two models for girls, a premenarchal model and a postmenarchal model (5). Following the modular paradigm of the new method, an alternative approach is used. When menarche occurs, it corresponds to a particularly accurate “tick-mark” on the girl's maturation axis, and the growth potential precisely at menarche is likely to be predictable. The menarche module in the new method contains the growth potential prediction as well as its uncertainty, and this knowledge is combined with other knowledge using Bayesian inference (see Appendix C for a worked example).

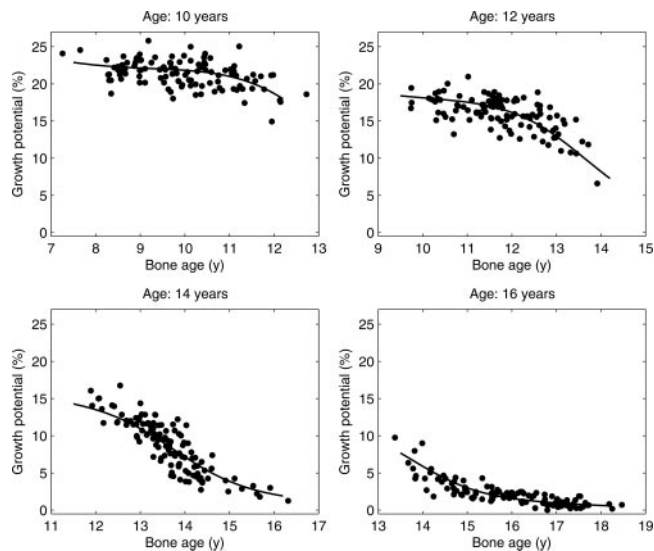
## Results

### Prediction from parents' heights

The height prediction model based on the parents' heights was found to  $H_p = 0.7884 H_{mid} + 42.2 \text{ cm} + sec$  for boys, and  $H_p = 0.7186 H_{mid} + 40.3 \text{ cm} + sec$  for girls, and the SD values of the prediction residuals were 5.9 and 4.3 cm, respectively. The secular trend was set to  $sec = 4 \text{ cm}$  for both sexes.

### The gp function estimation

The networks were fitted to the 3283 instances of  $gp$ , BA, and CA – BA, one for each gender. The used neural network methodology derives, from the training data, the optimal complexity of the neural network, expressed as the number of adjustable parameters. For boys, there are 21 parameters, whereas for girls there are only nine. Thus, the  $gp$  function is more nonlinear for boys. Figure 2 shows the fit to the data for a subset of the male data. An overview of the models is shown in Fig. 3, which displays the growth potential for fixed CA values. The  $gp$  prediction can be conveniently looked up graphi-



**FIG. 2.** The neural network fit to the *gp* of the data for boys of the 1ZLS at four selected ages.

cally from Supplemental Fig. 4 (published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>) and in Appendix E one can compare with the *gp* predictions of the Bayley-Pinneau model.

### The weights and prediction SD values

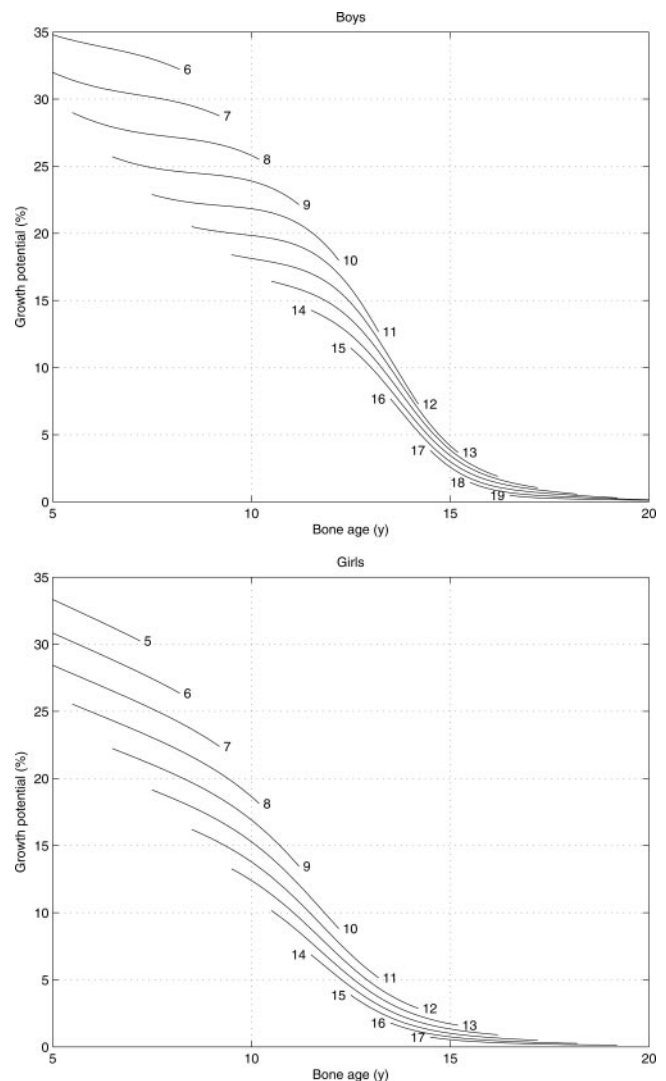
The weights used for combining the height predictions are listed in Supplemental Tables 4 and 5 (published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). Appendix B provides details on how the weights were estimated. The prediction errors of the models are also provided in Supplemental Tables 4 and 5, and they are all compared in Fig. 4.<sup>2</sup>

### BMI

The adult height prediction models derived so far were analyzed to see whether BMI can explain some of the residual variation, and Fig. 5 shows the height correction per BMI SDS. There is a pronounced effect for the boys, and the correction is negative with magnitude approximately 1.5 cm per BMI SDS up to approximately 13 yr. Thus, a boy with positive BMI SDS needs a negative correction of his adult height prediction and vice versa. For girls, the effect is small, at less than 0.5 cm per BMI SDS. Figure 5 also demonstrates that the correction looks similar when one uses the skinfold SDS instead of the BMI SDS.

### Menarche

The remaining height growth at menarche was found to be 6.6 cm with an SD of 2.2 cm.



**FIG. 3.** The learned *gp* function for all integer values of age for boys (top) and girls (bottom). The age is indicated next to each curve.

### A worked example

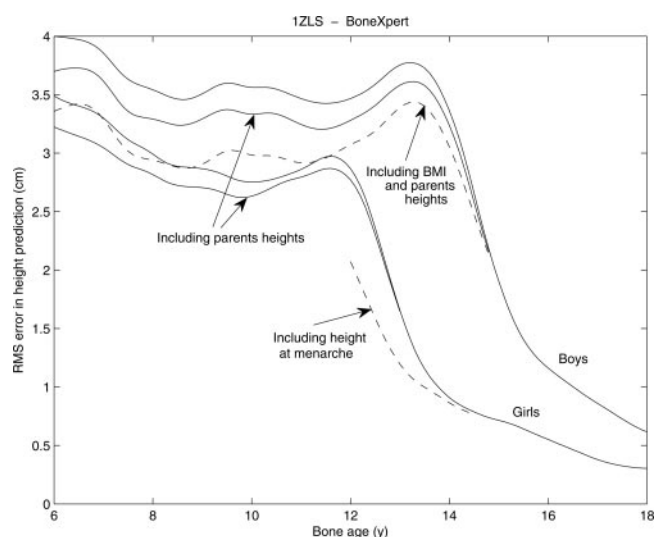
A boy of age 12.8 yr and BA 12.2 yr has, as determined from Supplemental Fig. 4, a growth potential prediction of 14.6%. With a current height of 167 cm, this yields a raw adult height prediction:  $H_{\text{raw}} = 167 \text{ cm} / (1 - 14.6/100) = 195.6 \text{ cm}$ .

The population mean  $H_{\text{pop}}$  is assumed to be 181 cm, and this mean is blended with a weight which, according to Supplemental Table 4, is 11.4%. The difference between  $H_{\text{raw}}$  and  $H_{\text{pop}}$  is 14.6 cm, and 11.4% of this difference is 1.7 cm. So the final result, with the SD also from Supplemental Table 4, is:  $H_{\text{pred}} = 193.9 \pm 3.6 \text{ cm} (\pm \text{SD})$ .

The parents are now measured as 175 and 189 cm, so the midparental height is 182 cm. The secular trend is

<sup>2</sup> The errors reported for the performance of the 1ZLS are the errors on the training set. We have performed a 10-fold cross-validation and hereby estimated that we expect the errors on an independent test set drawn from the same population to be 1.5% larger for both boys and girls, and we consider this effect negligible.





**FIG. 4.** The observed RMSEs of the new prediction models. There are two solid lines for each sex; the lower lines include parents' height. The dashed line for boys includes BMI and parents' height, whereas the dashed line for girls includes height at menarche (and not parents' height).

assumed to be 1 cm, so the height prediction from the parents is:  $H_p = 182 \text{ cm} \cdot 0.788 + 42.2 \text{ cm} + 1 \text{ cm} + (1 - 0.788)(181 - 178.2) \text{ cm} = 186.6 \text{ cm} + 0.212 \cdot 2.8 \text{ cm} = 187.2 \text{ cm}$ . According to Supplemental Table 4, this is combined with  $H_{\text{raw}}$  with a weight 21%, i.e.  $H_{\text{raw}}$  is corrected by 21% of 8.4 cm = 1.7 cm:  $H_{\text{predP}} = 193.9 \pm 3.4 \text{ cm}$ .

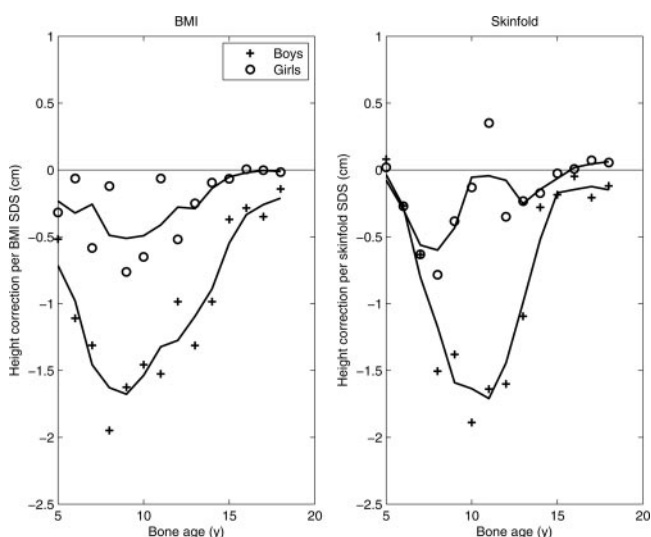
Finally, the boy has BMI = 18.8 kg/m<sup>2</sup>. According to Table 5 in Appendix F, BMI SDS = 1.0, and subtracting 1.3 cm, the best prediction becomes:  $H_{\text{predPW}} = 192.6 \pm 3.2 \text{ cm}$ .

### Validation study

The adult height of the children in the 3ZLS was defined as the height at the age of 18 plus a correction constant of 0.9 cm for boys and 0.3 cm for girls, where these constants were derived from the 1ZLS. The visits at age 18 yr were excluded from the validation data. The model predicts the adult height as well as the expected SD or RMSE uncertainty of the prediction, and the validation, shown in Fig. 6, compares the observed RMSE with the *expected* error.<sup>3</sup>

Averaging RMSE over the BA ranges 6–17 yr for boys and 6–15 yr for girls, we found that the actual (and predicted) errors were 3.1 (2.8) cm for the 432 observations for boys and 2.4 (2.4) cm for the 359 observations for girls. For the boy model using BMI, the errors were 3.1 (2.7) cm. The 95% confidence intervals were 0.4 cm wide, e.g. [2.9; 3.3] cm, so the difference between the observed and the expected RMSE was statistically significant for boys ( $P < 0.01$ ).

<sup>3</sup> Using the 1ZLS, we have found that for boys the error in predicting the height at 18 yr is a factor 1.11 smaller than the error in predicting the adult height, and 1.05 smaller for girls, and these factors have been applied in Fig. 6.



**FIG. 5.** The height correction to be applied to  $H_{\text{pred}}$  or  $H_{\text{predP}}$  to take BMI (left) or skinfold thickness (right) into account (the curves are a smoothed version of the year-by-year data).

### Discussion

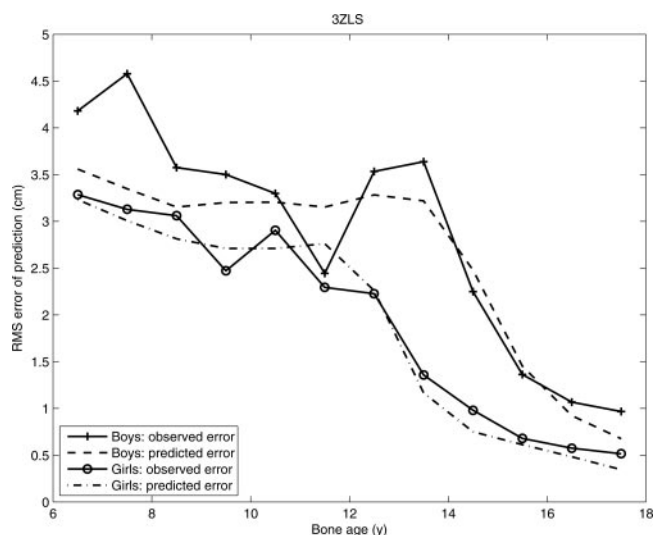
The prediction root mean square (RMS) errors shown in Fig. 4 exhibit a characteristic plateau that extends from 8 to 12.5 yr BA for boys and from 8 to 11 yr for girls. Inclusion of parents' heights lowers the RMSE by approximately 0.2 cm. The prediction error rises for boys at BA 12.5 yr and for girls at BA 11 yr. This is counterintuitive; one would expect the prediction accuracy to improve steadily as the target is approached. This phenomenon might be due to the large growth velocity at these ages: if BA is only an approximate estimate of the maturity of the axial skeleton, the resulting error in adult height prediction is correspondingly larger when the growth velocity is large. It implies that the child should preferably be examined *before* this BA, and recording a second x-ray at a later BA, where the error is larger, is of limited value.

The performance on the 3ZLS data used for validation was found to be as good as, or slightly worse than on the 1ZLS data. The median birth year of the 3ZLS is 1984, so these data represent present-day children, and it is satisfactory that a model estimated on their parents performed well on them.

### Other methods

The TW (5) and RWT (7) methods divide the prediction into bins of age (CA). For each value of CA, the adult height is modeled as a linear function of the form:  $H_{\text{pred}} = a(\text{CA}) \cdot b + b(\text{CA}) \cdot \text{BA} + c(\text{CA})$ .

Tanner used graphical methods to ensure that the co-



**FIG. 6.** The RMSE on the validation set of the adult height prediction in bins of bone age (solid lines), compared with the model's expectation of these errors (dashed and dash-dot lines).

efficients  $a$ ,  $b$ , and  $c$  vary gradually with CA, whereas RWT used mathematical smoothing methods. In the RWT method, there are also terms linear in the body weight and the midparental height.

The dependency on BA is linear through the term  $b(\text{CA}) \cdot \text{BA}$ . However, from Figs. 2 and 3, which consider the data at fixed CA values, we see that the dependence of  $gp$  on BA is nonlinear. At low BA, the curvature is negative, and at high BA it is positive, and it is obvious that  $H$  is, in general, a nonlinear function of BA for fixed CA and  $b$ . In other words, the TW and RWT methods oversimplify the BA dependence.

One could have extended the TW and RWT methods with nonlinear terms in  $b$  and BA, but this would be difficult to manage because the number of coefficients to be estimated would increase considerably. By dividing the model into modules, the new method can predict  $gp$  (BA, CA – BA) using nonlinear regression of only two variables, thereby keeping the number of parameters small; 21 for boys and nine for girls. The nonlinear modeling of  $gp$  is essential for covering the full spectrum of BA retardation and advancement. This is important because many of the children attending pediatric endocrinology have severely retarded or advanced BA.

### The absolute height models

The “raw” Bayley-Pinneau type height prediction,  $H_{\text{raw}}$ , is blind to the absolute size of the subject, and the role of the two absolute height modules is to moderate this raw prediction by adding knowledge about the absolute size of the subject.

The first model uses knowledge of the population mean,  $H_{\text{pop}}$ . Before puberty, the raw prediction is drawn approximately 13% of the way toward this mean. This implies that boys from The Netherlands ( $H_{\text{pop}} = 184$  cm) and Denmark ( $H_{\text{pop}} = 181$  cm) with the same  $H_{\text{raw}}$  will be attributed slightly different final height predictions. The difference is only 0.39 cm, but it illustrates the generality of the new framework. The carefully designed “draw” is essential for enabling the new method to cope with short, normal, and tall stature in the same model.

The absolute height module based on parents' heights works the same way, replacing  $H_{\text{pop}}$  by  $H_p$ . The draw is stronger, approximately 24% before puberty, because the prediction  $H_p$  is approximately twice as precise as  $H_{\text{pop}}$ . Bayesian inference (see Appendix B) predicts that these corrections are linear in  $b$ , which simplifies the modeling. The fact that the new method uses the same  $gp_{\text{pred}}$  model for predictions, with and without use of parents' height, is an advantage.

### Performance of the models

The new method and the TW3 methods for adult height prediction were both based on the 1ZLS, and this allows a direct comparison of their performances. The TW3 method was based on manual TW3 ratings (performed at the time of the study by a group of several experienced operators), and its performance is derived from Tables 10 and 12 in Ref. 6. The RMS error (RMSE) was averaged for the age range 10 to 15 yr for boys and 8 to 13 yr for girls. The RMSE of the new method (compared with the TW3 method) is 3.3 cm (3.5 cm) for boys and 2.7 cm (3.1 cm) for girls, *i.e.* the new method has slightly better performance with boys and significantly better performance with girls ( $P < 0.005$ ).<sup>4</sup> In other published work (18), we have shown that this performance gain is primarily due to the automated BA rating being more descriptive of the  $gp$  compared with manual TW3 rating. This is, of course, a very strong argument for the new method; even if one could rate as reliably as the TW raters in the 1ZLS with no rater bias relative to them, one would be outperformed by the new method. Including parents' heights improves the accuracy significantly for boys up to 13 yr and for girls up to 11 yr.

It is expected that this method, developed and validated on children from Zurich, will perform reasonably well on Caucasian children in other parts of the world, but this needs to be verified. For other ethnicities, the growth potential model may need to be reestimated.

Adult height prediction is less accurate for boys, but including BMI lowered the RMSE (between 10 and 15 yr) to

<sup>4</sup> We use the RMSE for the new model, whereas the TW3 model reported the prediction errors as sd values. Both models have very small biases in the 1ZLS data, and the difference between using sd error or RMSE is therefore negligible.

3.1 cm. Thus, prepubertal BMI seems to be a good predictor of the strength of the growth spurt in boys. Fat transforms androgens into estrogens accelerating maturation, in particular at puberty (see also Appendix F). However, caution should be made with this BMI correction because the causes of BMI variation today may be different from causes in the 1960s. Indeed, on the validation set, there was no advantage using the BMI correction, and it is therefore recommended not to use it in clinical practice until the role of BMI is better understood. Because the BMI correction is implemented as an add-on to the new model, it is easy to leave it out.

Up to a BA of 14 yr, it is advantageous to use the height at menarche, if it has occurred, and one does not need to measure the height exactly at menarche; one can determine it by interpolation.

## Conclusions

The new method performed significantly better than the TW3 method, mainly due to the superiority of the automatic BA rating in the new method.

The new method is designed to be bias-free in short and tall children and to cover children with very delayed and advanced BA. The tall and short children are accommodated by accurate design of the “drawing” toward the population mean, whereas very advanced and retarded BA are accommodated by a nonlinear growth potential function. Thus, it is reasonable to expect that the model will perform well on untreated subjects with idiopathic short stature, tall stature, constitutional delay of growth and puberty, as well as milder degrees of precocious puberty, but we have not studied this yet.

An elegant aspect of the new method is the inclusion of the parents' heights, BMI, and height at menarche in optional modules, *i.e.* they are not entangled with the main formula.

The new method is an exponent of evidence-based medicine, in the sense that it replaces a currently accepted subjective procedure with a more accurate, objective method. Organizing experience about growth and maturation across populations and conditions by means of the new method and adjusting the mathematical models if required by the data are a rational method for establishing a scientific basis for clinical decisions.

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