Introduction

The progression of sexual maturation, the pubertal growth spurt and menarche are linked to nutritional status [1–3]. If nutrition is inadequate, pubertal development is slowed, growth in stature stunted and menarche delayed. Adolescent girls who present with an eating disorder (ED) before menarche have not only lost weight but are also stunted in growth [4–9]. In an analysis of growth charts of such premenarcheal girls, we have shown that, in contrast to girls who have completed puberty before the onset of an ED, an inadequate weight gain and reduced growth velocity precedes presentation by years, which would indicate long-standing poor nutrition [8, 10]. To achieve full health and avoid the long-term health hazards associated with low circulating estrogen concentrations and amenorrhea, pubertal development must resume and eventually lead to menarche [11, 12]. During treatment of an ED in premenarcheal girls it is not sufficient only to regain lost weight. Since normal weight gain and growth have not been achieved for an extended period, weight deficit may be great even if weight loss proper at presentation is moderate [8]. Moreover, when growth and development is resumed, that in itself is associated with weight gain. In the course of treatment it would be desirable to predict menarche in order to set a target for treatment in terms of a weight or a weight range, which takes into account the ongoing development. Targets based on the weight for height and/or age of population standards do not take into consideration the natural variation, around an average, of weight and shape.
nor do they take into account the delayed development in girls with ED and primary amenorrhea. Standardized targets may therefore result in persisting amenorrhea despite what would appear as adequate weight gain. In order to be able to set individual weight targets during the early phase of treatment, we have presently analyzed weight requirements for menarche in girls with ED and primary amenorrhea. Prepuberal measurements of weight loss using growth charts from the school health services.

**Subjects and Methods**

**Subjects**

Case records of patients referred to the pediatric services of Uppsala University Children's Hospital for medical assessment of a suspected or diagnosed ED with onset before menarche were reviewed. During the period 1990 to September 2005, 76 such girls had been assessed. 14 girls had been lost to follow-up before menarche, 47 had reached menarche and 15 were amenorrhoic but still under treatment. In Sweden, school health services regularly monitor growth and weight gain from age 6 through 18. Copies of such growth charts were available for all the 47 patients, born in 1976–1993, who had reached menarche. One girl had diabetes, which was diagnosed, and under treatment before onset of the ED. Of the other girls, none developed a somatic disease during follow-up. Based on the history obtained at presentation, the diagnoses by DSM-IV [13] were either anorexia nervosa or an eating disorder not otherwise specified of the non-purging subtype. Vomiting was uncommon at presentation and no patient eventually received a diagnosis of bulimia nervosa. The protocol had been approved by the Ethics Committee of the Faculty of Medicine of Uppsala University.

**Analysis of Weight Change, Growth and Menstrual Status**

For all patients there were measurements of weight and stature at a maximal recorded weight, at presentation and at the lowest weight during the course of treatment. Prepubertal measurements of weight and stature were available from the growth charts of the school health services. When there were several measurements between ages 6 and 10 the earliest was used. In most cases this was a measurement obtained at a general health examination during the first year in school. Weight and stature throughout treatment and at menarche were obtained at visits to the Children's Hospital or the Eating Disorders Unit. If a visit was later than a month following menarche the weight and stature at the visits preceding and following menarche were used for interpolation. To analyze resumption of growth and pubertal development, weight gain and growth velocity were calculated for 1-year intervals preceding and following menarche for 41 of the girls. For most of the girls, measurements of height had not been performed sufficiently often to allow calculations of growth velocity for shorter time intervals.

Weights not recorded in case files or on growth charts or weights obtained at home were not used in the calculations. Body mass index (BMI) was calculated as weight/length$^2$ (kg/m$^2$) for all observations of weight and stature. Measures of weight, stature and BMI were recalculated into standard deviation scores (SDS) [14].

**Statistics**

Values are means ± SD. Differences in anthropometric indices between patients and the general population were analyzed by Student's two-tailed t test for independent samples. To predict the weight or BMI at menarche, a multiple stepwise regression analysis was used.

**Results**

The girls who presented with an ED and primary amenorrhea were, prior to onset of disease, heavier and less lean compared to the population mean as evidenced by SDS for weight and BMI above zero at a measurement before the start of puberty (table 1). At their top weight, SDS scores for weight, height and BMI did not differ from the population mean and there was thus a tendency of slowed weight gain and stunting of growth already at this

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**Table 1.** Anthropometric measures during the course of an ED with primary amenorrhea in 47 girls

<table>
<thead>
<tr>
<th></th>
<th>Prepubertal</th>
<th>At top weight</th>
<th>At presentation</th>
<th>At nadir</th>
<th>At menarche</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>7.7 ± 1.1</td>
<td>12.4 ± 1.6</td>
<td>13.3 ± 1.4</td>
<td>13.4 ± 1.6</td>
<td>15.5 ± 1.6</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>26.4 ± 3.7</td>
<td>41.7 ± 7.1</td>
<td>36.5 ± 6.2</td>
<td>35.5 ± 6.4</td>
<td>52.2 ± 5.3</td>
</tr>
<tr>
<td><strong>Length, cm</strong></td>
<td>127 ± 8</td>
<td>153 ± 8</td>
<td>156 ± 8</td>
<td>156 ± 9</td>
<td>163 ± 6</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>16.5 ± 1.7</td>
<td>17.8 ± 2.2</td>
<td>14.9 ± 1.7</td>
<td>14.6 ± 1.8</td>
<td>19.7 ± 1.9</td>
</tr>
<tr>
<td><strong>Weight (SDS)</strong></td>
<td>0.27 ± 0.90**</td>
<td>-0.32 ± 1.09NS</td>
<td>-1.83 ± 1.30***</td>
<td>-2.00 ± 1.49***</td>
<td>-0.29 ± 0.77*</td>
</tr>
<tr>
<td><strong>Length (SDS)</strong></td>
<td>-0.01 ± 1.08NS</td>
<td>-0.21 ± 1.16NS</td>
<td>-0.47 ± 1.43*</td>
<td>-0.56 ± 1.22**</td>
<td>-0.28 ± 1.19NS</td>
</tr>
<tr>
<td><strong>BMI (SDS)</strong></td>
<td>0.37 ± 0.78**</td>
<td>-0.30 ± 1.06NS</td>
<td>-2.2 ± 1.38***</td>
<td>-2.58 ± 1.50***</td>
<td>-0.21 ± 0.83NS</td>
</tr>
</tbody>
</table>

Values are means ± SD. BMI = Body mass index; SDS = standard deviation scores.
Significance of difference in comparison with population mean (i.e. SDS = 0): * p < 0.05; ** p < 0.01; *** p < 0.001; NS not significant.
stage. Indeed, 40/47 (85%) of the girls had decreased in weight SDS and 31/47 (66%) had decreased in height SDS up to their top weight. At presentation they had lost 5.1 ± 4.3 kg and grown only 2.8 ± 3.5 cm over 370 ± 235 days resulting in a stunting of growth by 0.32 ± 0.63 SDS. All girls had started puberty (Tanner stage ≥1 for breast and pubic hair) but attempts to stage puberty in greater detail on clinical examination had not been consistently performed. During the weeks immediately following presentation when treatment was initiated there was some further weight loss before weight gain and growth was established. The average duration from presentation to menarche was 30 ± 10 months. When weight gain was analyzed in 1-year periods in relation to menarche (fig. 1a) there was a weight loss 4 years prior to menarche corresponding to the period of weight loss before presentation. Three years before menarche, corresponding approximately to presentation and start of treatment, weight gain started and accelerated up to menarche after which it declined. Growth velocity (fig. 1b) was delayed in relation to weight gain. It declined from the fourth to the third year before menarche. Following start of weight gain 3 years before menarche, growth velocity peaked at 4.3 ± 2.6 cm/year 2 years before menarche and subsequently declined. Of the 41 girls thus analyzed, 2 peaked 3 years before, 29 2 years before and 10 the year before menarche. Menarche occurred at an age of 15.5 ± 1.6 years. The girls had then almost normalized weight and SDS for height and BMI did not differ from the population mean (table 1).

Menarche occurred within a wide weight range encompassing approximately 20 kg or 3 SDS (fig. 2) corresponding to a BMI range of 8 kg/m² or 3 SDS (data not shown). In order to predict menarche weight SDS at the different milestones of development and during the course of disease, and the age at menarche was entered as independent variable against weight SDS at menarche in a multiple stepwise regression analysis. In an initial bivariate analysis, all measures of weight were significantly associated with weight SDS at menarche (table 2). In the ensuing multivariate analysis an independent association with only prepubertal weight SDS remained. This association was highly significant (R² = 0.39; p < 0.001). The regression equation [weight SDS menarche] = 0.53 · [weight SDS prepubertal] – 0.43 indicates that menarche occurs at a weight SDS somewhat lower than the prepubertal weight SDS (fig. 3). When the regression was repeated with BMI SDS substituted for weight SDS predic-
The use of absolute terms of weight (kg) or BMI (kg/m²) in the regression was inferior in predicting menarche.

**Discussion**

The present investigation shows that weight gain, completion of the pubertal growth spurt and a normalization of body weight are necessary to reach menarche in young girls with ED and primary amenorrhea. Normalization of body weight is best described as returning to a normal growth track, i.e. the weight SDS of prepubertal development, a time point at which it is unlikely that the ED had influenced weight gain and growth. The growth track necessary for menarche should not be underestimated. Indeed, 17/47 (36%) of the girls had a weight above population average and 16/47 (34%) had a BMI above population average at menarche as evidenced by SDS > 0 for weight and BMI. The top weight SDS was close to the

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Predictors</th>
<th>Bivariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight SDS at menarche</td>
<td>Prepubertal weight SDS</td>
<td>0.39 &lt;0.001</td>
<td>0.39 &lt;0.001</td>
</tr>
<tr>
<td>Weight SDS at top weight</td>
<td>0.26 &lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Weight SDS at nadir</td>
<td>0.22 &lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>0.04 NS</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

SDS = standard deviation score; NS = not significant.
weight SDS at menarche. Top weight SDS, however, predicted menarche less well than the prepubertal weight SDS, is likely to have been influenced by the ED [8] and is thus less suitable as a target for treatment. A growth trajectory along the prepubertal weight SDS may therefore well represent the ‘true’ growth track of the individual.

The prepubertal growth track explained approximately 40% of the variation of weight at menarche. Other factors such as adiposity [15, 16] and biochemical signals related to fat mass, such as leptin, or linked to body size, such as insulin-like growth factor-1 [17–19] would probably add to the prediction of menarche but were presently not measured. Fat mass and biochemical markers are, however, associated with the weight gain and growth during pubertal development. The simplistic view to attempt to predict menarche by measures of weight at the outset of treatment is therefore practical in a clinical setting when a target for weight gain is to be set. This is possible despite the variation and errors inherent in measurements of weight and stature, an observation which strengthens the use of the present prediction model in clinical practice. The use of a growth track as the target for treatment is necessary in growing individuals since the expected weight increases with age as a consequence of normal growth and development. A target in absolute terms (kg) would then have to be repeatedly revised. A target in terms of a weight track (SDS) on a growth curve is easily understood and includes both the weight deficit to be recovered and the expected weight gain during normal growth.

Menarche was delayed by more than 2 years compared to healthy Swedish girls and the interval between peak growth velocity and menarche was longer than the expected 1-year period [20, 21]. It would thus appear that although weight gain accelerates growth, it takes a long time to fully reverse the effects of starvation on puberty. Moreover, net weight gain was achieved in all girls but the rate of weight gain may have been suboptimal and included periods of stagnation and even temporary weight loss. Although the sequence of events during puberty is the expected, progression is slower than in healthy girls. They may advance well through treatment, gain weight and gradually express less eating disordered psychopathology but menarche may be lagging. The present data would then suggest that the first thing to consider is whether weight gain is adequate and whether time sufficient to complete the growth spurt has elapsed. Two factors which are easily underestimated. If weight appears adequate in terms of return to a prepubertal growth track it is important to emphasize that continuing weight gain and growth along this trajectory is part of normal development and necessary for completion of puberty. The notion that puberty may not be completed can be corroborated by pelvic ultrasound to assess ovarian and uterine maturity [22]. To some girls the absence of menarche may be of great concern. An assessment by a gynecologist to rule out other causes of amenorrhea and assure normality may then be helpful. As menarche will eventually occur, reassurance and support will help the girls to stay in treatment, gain weight and grow until this goal is reached. This is of importance since long-standing amenorrhea affects physical health [11, 12] but also because persisting subnormal weight and amenorrhea may indicate persisting eating disturbed psychopathology, which needs to be addressed.

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References
