

# Obesity Among Children and Adolescents With Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

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## ABSTRACT

**OBJECTIVES.** Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the most common inherited disorder of adrenal steroid biosynthesis. Patients with the classic form of CAH show androgen excess, with or without salt wasting. There are few studies reporting on higher rates of overweight and obesity among children with CAH. In addition to its role in the regulation of energy balance, leptin is involved in various endocrine and metabolic pathways. In this context, elevated serum leptin levels were reported recently for patients with CAH and were thought to be involved in the development of obesity among these patients. Therefore, the aim of this study was to analyze BMI values, compared with population-based references, for children and adolescents with CAH. Possible contributing factors, such as glucocorticoid therapy, skeletal maturation, birth weight and length, and parental BMI, were correlated with current BMI SD scores (SDS). In addition, the implications of serum leptin levels, corrected for BMI, gender, and Tanner stage, were investigated.

**METHODS.** We performed a cross-sectional retrospective study of 89 children and adolescents with CAH (48 female and 41 male subjects; age: 0.2–17.9 years) who presented in our outpatient department during 1 year. All individuals had classic CAH, confirmed with molecular genetic analyses, and received substitution therapy (glucocorticoids and mineralocorticoids, if necessary). The quality of therapy was monitored in follow-up visits every 3 to 6 months, on the basis of clinical presentation and laboratory measurement findings according to current guidelines. We grouped the patients into salt wasting and simple virilizing groups, as well as according to current metabolic control. Leptin levels were measured with a commercial radioimmunoassay and calculated as SDS. For statistical analyses, standard parametric and nonparametric methods were used.

**RESULTS.** The chronologic ages of the children with CAH were between 0.20 and 17.9 years (mean  $\pm$  SD: 8.9  $\pm$  4.6 years). The BMI SDS of the whole group ranged from –2.7 to 4.3 (mean  $\pm$  SD: 0.88  $\pm$  1.3) and was significantly elevated above 0.

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### Key Words

congenital adrenal hyperplasia, 21-hydroxylase, obesity, leptin, BMI

### Abbreviations

CAH—congenital adrenal hyperplasia  
SV—simple virilizing  
SW—salt wasting

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Fifteen subjects (16.8%) had BMI SDS of  $>2.0$ , which indicated a significantly greater frequency of obesity among patients with CAH than expected for the normal population (expected: 2.27%). There was no significant difference in age and BMI between genders and clinical forms (salt wasting versus simple virilizing). BMI SDS was correlated positively with chronologic age. The BMI SDS did not differ significantly between children receiving hydrocortisone, prednisone, or dexamethasone. Hydrocortisone dosages (including equivalent dosages of prednisone and dexamethasone) ranged from 6.2 to 30.1 mg/m<sup>2</sup> body surface area (mean  $\pm$  SD: 14.7  $\pm$  4.8 mg/m<sup>2</sup> body surface area). Hydrocortisone dosages were correlated positively with BMI SDS. The relative risk of having a BMI SDS of  $>2.0$  was not significantly elevated among children with prednisone/dexamethasone medication, compared with those with hydrocortisone treatment. In contrast to this, fludrocortisone dosage was not correlated with BMI SDS. Bone age delay, as calculated from the difference of bone age and chronologic age, ranged from  $-2.9$  years to 5.6 years (mean  $\pm$  SD: 1.11  $\pm$  1.8 years) and was significantly elevated; it was correlated positively with BMI SDS. The BMI of parents ranged from 17.8 to 39.0 kg/m<sup>2</sup> (median: 24.2 kg/m<sup>2</sup>). Median BMI values did not differ significantly between fathers and mothers. The relative risk for obesity among our children (BMI SDS of  $>2.0$ ) was significantly elevated for children with obese parents, compared with those with nonobese parents (relative risk: 4.86). There was no significant correlation of birth length, birth weight, or gestational age with BMI SDS. Serum leptin values ranged from 0.10 to 32  $\mu$ g/L (median: 4.4  $\mu$ g/L); they were correlated positively with BMI SDS, chronologic age, and Tanner stage. After transformation into leptin concentration SDS values, the median SDS of 0.42 (range:  $-5.4$  to 3.1) did not differ significantly from 0.

**CONCLUSIONS.** Children and adolescents with CAH have a higher risk of obesity. Glucocorticoid dosage, chronologic age, advanced bone age maturation, and parental obesity contributed to elevated BMI SDS, whereas birth weight and length, serum leptin levels, used glucocorticoid, and fludrocortisone dosage were not associated with obesity. Therefore, children with CAH who become obese should be tightly monitored and should participate concurrently in weight management programs that include obese family members.

**C**ONGENITAL ADRENAL HYPERPLASIA (CAH) due to 21-hydroxylase deficiency is the most common inherited disorder of adrenal steroid biosynthesis. Patients with the classic form of CAH exhibit androgen excess, with or without salt wasting (SW). Inadequate therapy may cause short-term and long-term complications, such as electrolyte imbalances, Addisonian crises, accel-

erated bone maturation, short stature, hirsutism and virilization, and decreased fertility.<sup>1,2</sup> In this context, some studies reported higher rates of overweight and obesity among patients with CAH. In one of the first studies, Knorr and Hinrichsen-de-Lienau<sup>3</sup> found a significant relationship between overtreatment with hydrocortisone during the first 2 years of life and later development of obesity among young adults. Cornean et al<sup>4</sup> described significantly increased BMI values for patients with CAH between 5 and 10 years of age, compared with the BMI at the age of 1 year.

Leptin is thought to be part of an adipostat signaling satiety to the brain. In addition to this role in the regulation of energy balance, leptin is involved in various endocrine and metabolic pathways. Serum levels are controlled primarily by fat mass and androgens.<sup>5</sup> However, it has been shown that glucocorticoids can act as a positive regulator of leptin, which indicates a definite association with the hypothalamic-pituitary-adrenal axis. Elevated serum leptin levels among patients with CAH were reported recently.<sup>6,7</sup>

Therefore, the aim of this study was to analyze BMI values, transformed to population-based SD scores (SDS), among children and adolescents with CAH. Possible contributing factors, such as glucocorticoid therapy, skeletal maturation, birth weight and length, and parental BMI, were correlated with current BMI SDS. In addition, the implications of serum leptin levels corrected for BMI, gender, and Tanner stage were investigated.

## METHODS

### Patients

We studied 89 Bavarian children and adolescents with CAH (48 female patients and 41 male patients), between 0.2 and 17.9 years of age, who presented regularly at our outpatient endocrine unit (Bavaria is a federal state in the south of Germany and has  $\sim$ 12 million inhabitants). All individuals had classic CAH with 21-hydroxylase deficiency, as confirmed with molecular genetic analyses. All received glucocorticoid substitution therapy with hydrocortisone ( $n = 73$ ), prednisone ( $n = 12$ ), or dexamethasone ( $n = 4$ ). The quality of therapy was monitored in follow-up visits every 3 to 6 months, on the basis of clinical presentation and laboratory measurements according to current guidelines (follow-up period: median: 5.3 years; range: 0.2–18 years).<sup>8</sup> At the time of the analysis, none of the patients had obvious signs of any acute or chronic disease or received any other medication.

Because genotype-phenotype correlations in CAH are difficult, we grouped our patients as having simple virilizing (SV) or SW disease in 2 different ways, ie, according to their initial clinical presentation (group 1: SW: total: 78 patients; female: 44 patients; male: 34 patients; SV: total: 11 patients; female: 4 patients; male: 7 pa-

tients) and according to the need for fludrocortisone substitution on the basis of elevated serum renin concentrations at the time of analysis, because some patients with SV disease over time developed mineralocorticoid insufficiency (group 2: SW: total: 85 patients; female: 46 patients; male: 39 patients; SV: total: 4 patients; female: 2 patients; male: 2 patients). All comparisons between SV and SW groups were calculated with both models.

Clinical control was classified according to the modified criteria described previously,<sup>9,10</sup> on the basis of the presence of 1 major or 2 minor criteria. Major signs of poor metabolic control were progressive virilization, intervals of >6 months (<12 years of age) or >12 months (>12 years of age) between visits at our outpatient endocrine unit, increased urinary excretion of pregnanetriol, exceeding the reference limits published by Knorr and Hinrichsen-de-Lienau,<sup>3</sup> or height velocity SDS of >2.0; minor signs of poor metabolic control were height velocity SDS of >2 but decreasing, change in bone age relative to change in chronologic age of >1.5 (prepubertal) or >2.5 (pubertal), serum 17-hydroxyprogesterone concentrations of >10 µg/L, or serum renin concentrations above the 95% confidence interval.<sup>11,12</sup>

Major signs of overtreatment were Cushing signs, maintained or progressive, height velocity SDS less than -2 and decreasing, or urinary excretion of pregnanetriol below the reference limits; minor signs were height velocity SDS less than -2, maintained or increasing, serum 17-hydroxyprogesterone concentrations of <0.1 µg/L, or serum renin concentrations below the 5% confidence interval. Urinary creatinine levels were also measured, to assess collection completeness. According to these criteria, 64 patients (72.0%) had optimal metabolic control, 17 (19.1%) had poor metabolic control, and 8 (9.0%) demonstrated overtreatment.

### Study Protocol

The cross-sectional data for all patients were ascertained during regular follow-up visits to our outpatient endocrine unit. The data were collected retrospectively for all patients who presented themselves during the 12-month period between January and December 2004. The data analysis was approved by our institutional review board and the local ethics committee. Physical examinations included evaluation of height, weight, blood pressure, and pubertal status. Body height was measured with a Harpenden stadiometer. Height SDS were calculated by using German references.<sup>13</sup> Body weight was determined without clothes (except underwear) with a digital weight scale. BMI and SDS were calculated and adjusted for age and gender according to current German reference data.<sup>14</sup> According to the Childhood Group of the International Obesity Task Force, a BMI SDS of >2.0 was defined as obesity.<sup>15-17</sup> For 80 children, parental data on height and weight were assessed with the same methods. On the basis of World Health Organization guide-

lines, we chose a BMI of >30 kg/m<sup>2</sup> as the cutoff value for the definition of obesity among adults.<sup>18</sup> Equivalent hydrocortisone dosages were calculated for prednisone and dexamethasone (factors 4 and 30, respectively). Data on birth length, birth weight, and gestational age were available for 77 children. SDS were determined according to Swedish data.<sup>19</sup> For a subgroup of children ( $n = 74$ ), bone age was assessed by an experienced observer with the atlas method of Greulich and Pyle, which was found to be reliable for central European children.<sup>20</sup> For evaluation of the current status of skeletal maturation, we calculated the difference between bone age and chronologic age (bone age delay = bone age minus chronologic age, in years). Routine blood sampling was performed to monitor the therapy. Serum was then separated by centrifugation and stored at -20°C until assayed.

Leptin levels were measured in the residuals of these serum samples for a subgroup of 54 patients with CAH (age: 0.2-17.9 years; median: 9.0 years), with a radioimmunoassay (Mediagnost, Reutlingen, Germany). The intraassay coefficient of variation was 7.3%, and the level of sensitivity was 32 ng/L. Leptin concentration SDS were calculated according to the method described by Blum et al,<sup>21</sup> because our leptin assay method was the same.

### Statistical Analyses

Normality was tested with the Shapiro-Wilk test ( $P > .05$ ). Chronologic age, BMI SDS, hydrocortisone dosage, bone age delay, birth length SDS, and birth weight SDS had gaussian distributions, whereas gestational age, parental BMI, fludrocortisone dosage, and leptin values (in micrograms per liter and SDS) did not. Nonlinear regression analysis for a gaussian distribution model was performed for BMI SDS.

To compare each variable between genders and clinical forms (SV or SW), unpaired  $t$  tests, including  $F$  tests for comparison of variances, and Mann-Whitney  $U$  tests were used where appropriate. To assess significant deviations from a hypothetical value, we used 1-sample  $t$  tests and Wilcoxon signed-rank tests. For analysis of relationships between 2 parameters, Pearson ( $r_p$ ) and Spearman ( $r_s$ ) correlation coefficients were assessed. For variables with normal distribution, linear correlation analyses were applied. To evaluate potential risk factors, specific 2 × 2 contingency tables were built and relative risks and odds ratios were calculated. For the determination of  $P$  values, we used Fisher's exact test. Observed and expected frequencies were compared with the standard binomial test. All tests were 2-sided, and  $P < .05$  was considered to be significant. For calculation and presentation, we used GraphPad Prism software, version 4.02 (GraphPad, San Diego, CA).

## RESULTS

### Patient Group

The chronologic age of the children with CAH was between 0.20 and 17.9 years (median: 8.7 years; mean  $\pm$  SD:  $8.9 \pm 4.6$  years). Detailed birth data are shown in Table 1. The BMI SDS of the whole group ranged from  $-2.7$  to  $4.3$  (mean  $\pm$  SD:  $0.88 \pm 1.3$ ) and was elevated significantly above 0 ( $P < .0001$ ) (Fig 1). Fifteen subjects (16.8%; female: 7; male: 8) had a BMI SDS of  $>2.0$ , which indicated a significantly greater frequency of obesity among patients with CAH than expected for the normal population (expected: 2.27%;  $P < .0001$ ) (Fig 1). There was no significant difference in age or BMI between genders and clinical forms (SW versus SV). BMI SDS was correlated positively with chronologic age (Table 2 and Fig 2).

### Glucocorticoid Therapy

The BMI SDS did not differ significantly among children receiving hydrocortisone, prednisone (prednisone), or dexamethasone. Hydrocortisone dosages (including equivalent dosages of prednisone and dexamethasone) ranged from 6.2 to 30.1 mg/m<sup>2</sup> body surface area (mean  $\pm$  SD:  $14.7 \pm 4.8$  mg/m<sup>2</sup> body surface area). There was no significant difference between genders. Hydrocortisone dosages were correlated positively with BMI SDS (Table 2 and Fig 2). For the subgroup of patients  $>5$  years of age, equivalent hydrocortisone dosages during the first 1 year of life did not correlate with later BMI SDS. Only 1 of the obese patients had received a hydrocortisone dosage of  $>30$  mg/m<sup>2</sup> body surface area during the first 2 years of life. The relative risk and odds ratio of having a BMI SDS of  $>2.0$  were not elevated significantly among children with prednisone/dexamethasone

**TABLE 1 Clinical Data**

	Female (n = 48)	Male (n = 41)	Total (n = 89)	P
Chronologic age, y				
Median (range)	8.90 (0.60–17.9)	8.40 (0.20–17.3)	8.70 (0.20–17.9)	NS
Mean $\pm$ SD	9.18 $\pm$ 4.40	8.49 $\pm$ 5.02	8.86 $\pm$ 4.68	
Length/height, SDS				
Median (range)	$-0.32$ ( $-2.52$ to $1.09$ )	$0.13$ ( $-2.02$ to $3.92$ )	$-0.15$ ( $-2.52$ to $3.92$ )	.046 <sup>a</sup>
Mean $\pm$ SD	$-0.39 \pm 0.99$	$0.23 \pm 1.41$	$-0.10 \pm 1.23$	.018 <sup>b</sup>
BMI, SDS				
Median (range)	$0.91$ ( $-2.66$ to $3.84$ ) <sup>c</sup>	$1.06$ ( $-1.66$ to $4.29$ ) <sup>c</sup>	$0.98$ ( $-2.66$ to $4.29$ ) <sup>c</sup>	NS
Mean $\pm$ SD	$0.75 \pm 1.37$ <sup>d</sup>	$1.03 \pm 1.31$ <sup>d</sup>	$0.88 \pm 1.34$ <sup>d</sup>	
HC dosage, mg/m <sup>2</sup>				
Median (range)	13.4 (6.21–27.1)	15.4 (8.10–30.1)	13.8 (6.21–30.1)	NS
Mean $\pm$ SD	13.9 $\pm$ 3.99	15.9 $\pm$ 5.36	14.8 $\pm$ 4.76	
FC dosage, $\mu$ g/m <sup>2</sup>				
Median (range)	58.5 (20.0–227)	65.0 (0.0–181)	59.0 (0.0–227)	NS
Mean $\pm$ SD	60.8 $\pm$ 33.5	65.8 $\pm$ 44.5	63.1 $\pm$ 38.8	
Bone age delay, y				
Median (range)	$0.30$ ( $-2.90$ to $4.20$ ) <sup>e</sup>	$1.40$ ( $-1.00$ to $5.60$ ) <sup>c</sup>	$0.80$ ( $-2.90$ to $5.60$ ) <sup>c</sup>	.010 <sup>a</sup>
Mean $\pm$ SD	$0.58 \pm 1.56$ <sup>f</sup>	$1.75 \pm 1.88$ <sup>d</sup>	$1.13 \pm 1.80$ <sup>d</sup>	.005 <sup>b</sup>
Birth length, SDS				
Median (range)	$0.19$ ( $-2.56$ to $4.46$ )	$0.22$ ( $-3.28$ to $4.36$ )	$0.21$ ( $-3.28$ to $4.46$ ) <sup>e</sup>	NS
Mean $\pm$ SD	$0.38 \pm 1.36$	$0.39 \pm 1.57$	$0.39 \pm 1.45$ <sup>f</sup>	
Birth weight, SDS				
Median (range)	$-0.40$ ( $-2.44$ to $1.72$ )	$-0.41$ ( $-2.14$ to $2.06$ )	$-0.41$ ( $-2.44$ to $2.06$ ) <sup>e</sup>	NS
Mean $\pm$ SD	$-0.38 \pm 0.99$	$-0.24 \pm 1.12$	$-0.31 \pm 1.05$ <sup>g</sup>	
Gestational age, wk				
Median (range)	40 (31–42)	40 (31–42)	40 (31–42)	NS
Mean $\pm$ SD	39.3 $\pm$ 1.97	39.3 $\pm$ 1.96	39.3 $\pm$ 1.95)	
Serum leptin concentration, $\mu$ g/L				
Median (range)	4.5 (0.10–32.0)	3.1 (0.10–29.0)	4.4 (0.10–32.0)	NS
Mean $\pm$ SD	7.4 $\pm$ 8.08	6.9 $\pm$ 9.48	7.2 $\pm$ 8.54	
Serum leptin concentration, SDS				
Median (range)	$-0.12$ ( $-5.44$ to $2.32$ )	$0.71$ ( $-4.61$ to $3.06$ )	$0.42$ ( $-5.44$ to $3.06$ )	NS
Mean $\pm$ SD	$-0.48 \pm 1.94$	$0.35 \pm 1.95$	$-0.17 \pm 1.96$	

NS indicates not significant for  $P < .05$ ; HC, hydrocortisone; FC, fludrocortisone.

<sup>a</sup>Mann-Whitney *U* test, female versus male.

<sup>b</sup>Unpaired *t* test, female versus male.

<sup>c</sup>Significantly different from 0 (Wilcoxon signed rank test),  $P < .001$ .

<sup>d</sup>Significantly different from 0 (1-sample *t* test),  $P < .001$ .

<sup>e</sup>Significantly different from 0 (Wilcoxon signed rank test),  $P < .05$ .

<sup>f</sup>Significantly different from 0 (1-sample *t* test),  $P < .05$ .

<sup>g</sup>Significantly different from 0 (1-sample *t* test),  $P < .01$ .

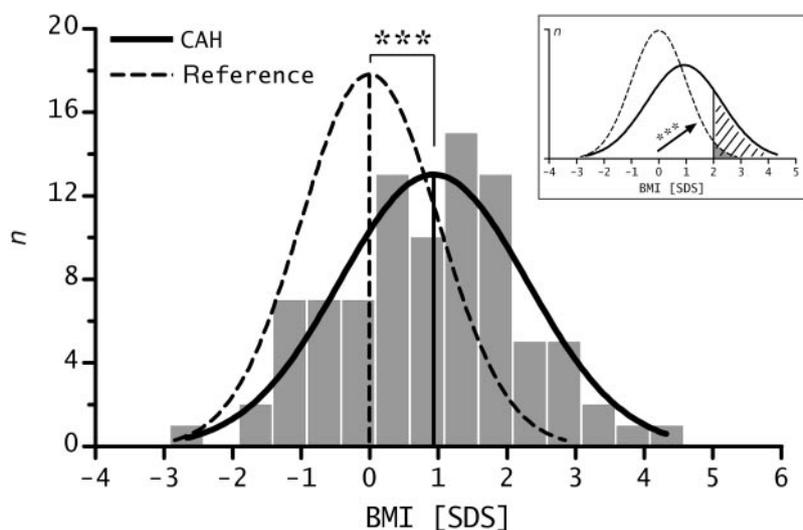


FIGURE 1

Distribution of BMI values (SDS) among patients with CAH (solid line), compared with the German reference population (dashed line)  $\left[ y = \frac{44.70}{\sqrt{2\pi}} \cdot \exp^{-1/2x^2} \right]$ . The main graph presents a histogram of BMI values in CAH and a calculated graph of a gaussian distribution model (nonlinear regression analysis)  $\left[ y = \frac{44.70}{1.369 \cdot \sqrt{2\pi}} \cdot \exp^{-\frac{1}{2} \left( \frac{x-0.929}{1.369} \right)^2} \right]$ , with a significant ( $P < .0001$ ) shift of the mean; inset, significantly increased area for BMI SDS of  $>2.0$  ( $P < .0001$ ).

TABLE 2 Correlation of Different Variables With BMI (SDS)

BMI (SDS) With	Unit	Correlation Coefficient	95% CI	P
Bone age delay	y	$r_p = 0.536$	0.349 to 0.682	<.0001
Chronologic age	y	$r_p = 0.222$	0.014 to 0.411	.0368
HC dosage	mg/m <sup>2</sup>	$r_p = 0.218$	0.011 to 0.408	.0397
FC dosage	μg/m <sup>2</sup>	$r_s = -0.189$	-0.387 to 0.027	NS
Birth length	SDS	$r_p = 0.012$	-0.213 to 0.235	NS
Birth weight	SDS	$r_p = 0.118$	-0.105 to 0.329	NS
Gestational age	wk	$r_s = 0.119$	-0.109 to 0.334	NS
Serum leptin concentration	SDS	$r_s = -0.098$	-0.363 to 0.182	NS

NS indicates not significant for  $P < .05$ ; CI, confidence interval; HC, hydrocortisone; FC, fludrocortisone.

medication, compared with those with hydrocortisone treatment, although 9 of 11 children whose equivalent hydrocortisone dosage was  $>20$  mg/m<sup>2</sup> body surface area received prednisone (Table 3). In contrast to this, fludrocortisone dosages were not correlated with BMI SDS (Table 2).

### Skeletal Maturation

Bone ages ranged from 6 months to 18.0 years (mean  $\pm$  SD:  $9.4 \pm 4.3$  years). Bone age delay, as calculated from the difference between bone age and chronologic age, ranged from  $-2.9$  years to 5.6 years (mean  $\pm$  SD:  $1.11 \pm 1.8$  years) and was elevated significantly ( $P < .0001$  for  $>0$  years; not significant for  $>1.0$  year). Seven of 11 patients who presented clinically with SV disease were male. Because these boys were diagnosed later, bone age was probably significantly more accelerated among boys than among girls. Height SDS might be greater for boys than for girls for the same reasons (Table 1). For the

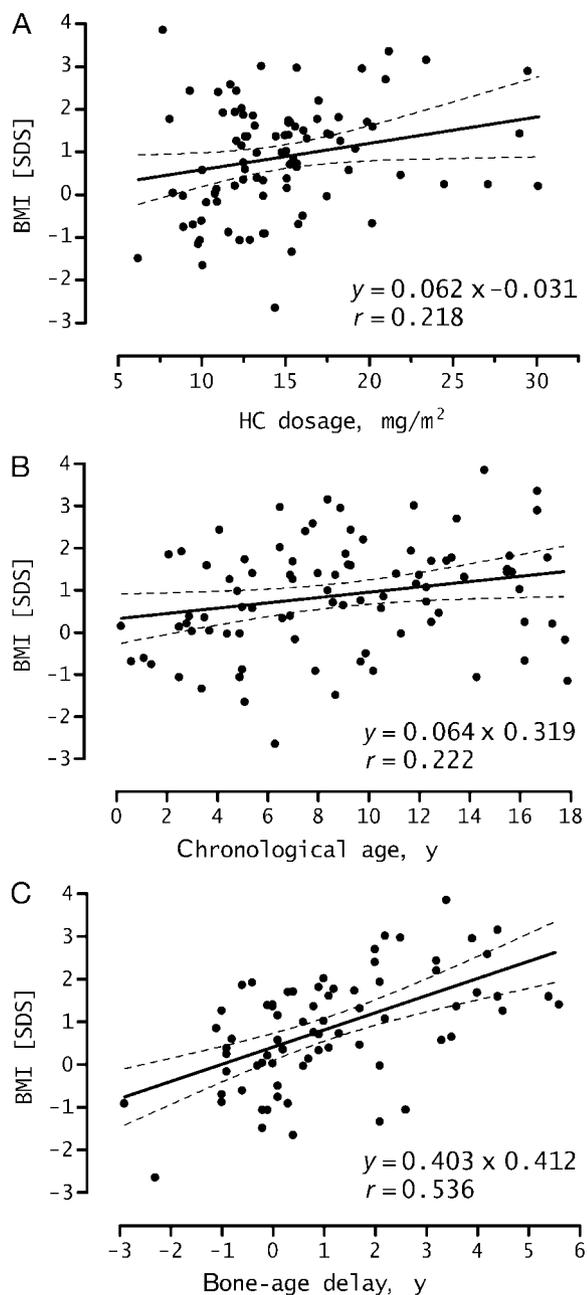
whole group, bone age delay was correlated positively with BMI SDS (Table 2 and Fig 2) but showed no significant correlation with chronologic age. A subgroup analysis in relation to pubertal development (Tanner stage 1,  $n = 50$ , versus Tanner stages 2–5,  $n = 25$ ) showed significantly more elevated bone age in cases with an advanced Tanner stage ( $P = .034$ ). In both subgroups, however, a significant correlation between bone age delay and BMI SDS was shown (Tanner stage 1:  $r_p = 0.488$ ,  $P = .0003$ ; Tanner stages 2–5:  $r_p = 0.556$ ,  $P = .0039$ ).

### Parental BMI

BMI of parents ranged from 17.8 to 39.0 kg/m<sup>2</sup> (median: 24.2 kg/m<sup>2</sup>). Ten percent ( $n = 8$ ) of the mothers and 7.5% ( $n = 6$ ) of the fathers were obese (ie, BMI of  $>30$  kg/m<sup>2</sup>). Median BMI values did not differ significantly between fathers and mothers. A total of 17.5% ( $n = 14$ ) of the children studied had  $\geq 1$  obese parent; however, none of the children in our cohort had 2 obese parents. The relative risk and odds ratio for obesity (BMI SDS of  $>2.0$ ) among our children were significantly elevated for children with obese parents, compared with children with nonobese parents (Table 3).

### Birth Auxology

Birth length SDS ranged from  $-3.2$  to 4.5 (mean  $\pm$  SD:  $0.39 \pm 1.45$ ) and birth weight SDS ranged from  $-2.4$  to 2.1 (mean  $\pm$  SD:  $-0.31 \pm 1.04$ ). Birth length was significantly greater and birth weight was significantly lower, compared with SDS of 0 (Table 1). All children were born between the 31st and 42nd weeks of gestation (median: 40 weeks; 6 infants [6.7%] were premature, ie,



**FIGURE 2** Linear regression analyses of relationships of equivalent hydrocortisone (HC) dosage (A), chronological age (B), and bone age delay (C) with BMI SDS. Each linear equation (continuous line) is shown with the 95% confidence interval (dashed lines) and Pearson correlation coefficient.

<37th week of gestation). There were no significant differences between male and female subjects and between the SW and SV forms for the 3 variables. There was also no significant correlation between birth length, birth weight, and gestational age and current BMI SDS (Table 2).

#### Serum Leptin Concentrations

Serum leptin concentrations ranged from 0.10 to 32  $\mu\text{g/L}$  (median: 4.4  $\mu\text{g/L}$ ). They were correlated positively

with BMI SDS, chronological age, and Tanner stage (Table 4). There was no significant difference between girls and boys. After transformation into leptin concentration SDS according to the method described by Blum et al,<sup>21</sup> the median SDS of 0.42 (range:  $-5.4$ – $3.1$ ) did not differ significantly from 0. There was no significant difference between the 2 clinical forms and no significant correlation between BMI SDS and serum leptin concentration SDS. Furthermore, there was no correlation between hydrocortisone dosage and serum leptin concentration SDS.

#### DISCUSSION

Our data clearly showed an increased risk of obesity among children and adolescents with classic CAH due to 21-hydroxylase deficiency, compared with the German reference population. Current data on obesity ascertained at Bavarian school entry examinations revealed a slightly increased prevalence for obesity (2.9%, compared with the expected value of 2.3%)<sup>22</sup> but complied with British reference values.<sup>23</sup> Because current German references,<sup>14</sup> published several years later, showed a markedly higher 97th percentile, in comparison with British children, we presume that the difference in prevalence of 0.6% is not significant. Therefore, our observations regarding an increased rate of obesity in CAH do not simply reflect the general trend toward higher BMI values in industrialized countries.

In the late 1980s, Knorr and Hinrichsen-de-Lienau<sup>3</sup> reported an increased rate of obese patients with CAH among those who were treated inadequately with high glucocorticoid dosages (expressed as hydrocortisone equivalents because not only hydrocortisone but also prednisone, prednisolone, and triamcinolone had been used) during the first years of life. In that study, obesity was defined not as BMI SDS of  $>2.0$  but as weight-for-height index of  $>115\%$ . Seventy-five percent of the overtreated children developed obesity after their 6th year of life.<sup>3</sup> In our cohort, we found 15 obese patients (16.5%), all receiving hydrocortisone, but only 1 of them had been treated with an inadequately high hydrocortisone dosage during the first 6 months of life. In contrast to Knorr and Hinrichsen-de-Lienau,<sup>3</sup> we found an increased obesity rate among children who were not overtreated with hydrocortisone, too. However, we found a slight but significant positive correlation of BMI with the current hydrocortisone dosage.

Cornean et al<sup>4</sup> found increasing BMI SDS values during the first 5 years of age for patients with CAH ( $n = 13$ ), together with a significantly greater skinfold thickness, as an indicator of fat mass. Those authors suggested that an earlier “adiposity rebound,” ie, increasing BMI during late childhood, took place earlier among children with CAH. Roche et al<sup>24</sup> also described elevated BMI SDS values ( $n = 38$ ; 6.1–18.2 years of age) but found no correlation between BMI and chronological age. In con-

**TABLE 3** Relative Risks and Odds Ratios of Obesity (ie, BMI SDS of > 2.0)

	RR	95% CI of RR	OR	95% CI of OR	P (Fisher)
Parental obesity <sup>a</sup>	4.86	2.02–11.7	8.71	2.36–32.2	<.0001
PR/DX substitution <sup>b</sup>	0.134	0.902–5.76	2.86	0.820–9.99	NS
Poor metabolic control	0.970	0.381–2.47	0.963	0.307–3.02	NS

RR indicates relative risk; OR, odds ratio; CI, confidence interval; PR, prednisone; DX, dexamethasone; NS, not significant for  $P < .05$ .

<sup>a</sup> At least 1 parent had BMI of >30 kg/m<sup>2</sup>.

<sup>b</sup> Compared with patients with hydrocortisone substitution.

**TABLE 4** Correlation of BMI, Chronologic Age, and Tanner Stage With Serum Leptin Concentration

Leptin Concentration (μg/L) With	Unit	Correlation Coefficient (r <sub>s</sub> )	95% CI	P
BMI	SDS	0.710	0.541–0.824	<.0001
Chronologic age	y	0.464	0.216–0.655	.0004
Tanner stage	No.	0.349	0.0815–0.570	.0097

CI indicates confidence interval.

trast to this, we found a weak but positive correlation of BMI with age in our cohort, which might be attributable to the larger number of patients studied and the consideration of a broader age range.

During the past years, the impact of low birth weight on adult life has become the subject of research. There seems to be alternative programming during the fetal period that leads to higher risks for small-for-gestational age infants to develop adult diseases, such as hypertension, cardiovascular disease, and metabolic syndrome.<sup>25,26</sup> Interestingly, there is also evidence of an involvement of the hypothalamic-pituitary-adrenal axis.<sup>27</sup> Among our children with CAH, we did not find any relationship between birth weight or length and current BMI.

Generally, the effectiveness of glucocorticoid therapy over a period of years is difficult to assess. Monitoring of serum and urinary laboratory measures covers only a few days or weeks, whereas accelerated skeletal maturation as an index of poor metabolic control might be more representative over a longer time. Results from a retrospective, multinational study of 341 patients with CAH showed significant bone age acceleration, but BMI or other weight values were not reported.<sup>28</sup>

Among our patients, bone age delay was not correlated with chronologic age, but it was significantly more advanced among pubertal children with CAH than among their prepubertal peers. This might be related to the gradual increase of gonadal steroid production or might reflect lower compliance during puberty. Cornean et al<sup>4</sup> also reported on accelerated bone maturation in the context of increased BMI. In agreement, we found a positive correlation between bone age delay and BMI SDS in our cohort.

We identified parental obesity as another important factor contributing to obesity among children with CAH. To the best of our knowledge, there are no previous

studies analyzing parental BMI in CAH. However, it remains unclear which specific factors contribute to this finding. According to large-scale epidemiologic studies, “true” heritability of obesity is contributive in 25% to 40% of cases.<sup>29,30</sup> The contribution of the heterozygous carrier status must also be taken into account. In addition, the influence of individual lifestyles, such as sports and nutrition, on obesity is obvious.<sup>18</sup>

In recent years, there has been an enormous effort to identify factors contributing to the regulation of energy balance.<sup>31</sup> Leptin has been suggested to play a major role in the regulation of satiety and obesity.<sup>32</sup> There have been reports of increased plasma leptin levels after administration of dexamethasone among healthy adults, as well as patients with Cushing’s syndrome,<sup>33</sup> and reports that leptin reduces the release of corticotropin-releasing hormone and corticotropin.<sup>34,35</sup>

Recently, Charmandari et al<sup>7</sup> reported significantly higher BMI values together with elevated serum leptin and insulin levels and reduced catecholamine levels for 18 patients with CAH, compared with healthy control subjects. Those authors speculated that these hormones are part of a complex process of interfering hormones resulting in additional increases in androgen production. In another study, elevated serum leptin levels were reported after the start of glucocorticoid therapy for patients with CAH.<sup>6</sup> We do not doubt these results, because we also measured higher serum leptin levels in our cohort. However, we have concerns regarding the methods used, because neither the BMI values nor the leptin data were converted into population-based SDS corrected for age and gender. After exclusion of factors contributing to elevated leptin levels, with calculation of leptin level SDS corrected for population, age, and gender, the previously significant elevation of leptin concentrations disappeared.

## CONCLUSIONS

Children and adolescents with CAH have a higher risk of obesity. Glucocorticoid dosage, chronologic age, advanced bone age maturation, and parental obesity contributed to elevated BMI SDS, whereas birth weight and length, serum leptin levels, glucocorticoids used, and fludrocortisone dosage were not associated with obesity. Because our cross-sectional study covers only 1 time point per patient, there is a need for longitudinal studies analyzing the different factors contributing to the devel-

opment of obesity. Our data define obese children with CAH, particularly in association with parental obesity, as a special cohort of patients who require close monitoring and integration in weight management programs.

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